MECHANISTIC RATIONALE OF PSEUDOEPHEDRINE AS A CHIRAL AUXILIARY: NMR INVESTIGATION AND SYNTHESIS OF NOVEL AUXILIARIES

By

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A thesis submitted to the WestCHEM, Department of Pure and Applied Chemistry, University of Strathclyde in part fulfilment of regulations for the degree of Master of Philosophy
2011

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Signed: Camille Indey

Date: 1/12/2011

Acknowledgments

First of all, I would like to acknowledge Dr Colin Gibson for welcoming me as his student and for his advice, help and most of all encouragements during the whole year of this project.

I would also like to thank Dr John Parkinson for his advice and expertise on the NMR studies as well as Craig Irving. I also thank Dr Alan Kennedy for giving us access to (1*R*,2*R*)-pseudoephedrine and Prof. Colin Suckling for his advice.

I would also like to acknowledge everyone in TG416 from Prof. Colin Suckling's group for a good work atmosphere and especially Dr Craig McInnes for his lab advice and Fraser Scott for his help on molecular modeling.

Furthermore, I would like to thank Prof. Anthony Smith and Mrs. Catherine Ponthus from my home school CPE Lyon for their support and help. Dr Debbie Willison from the University of Strathclyde has also been a great help regarding administrative paperwork.

Last but not least I would like to thank Benoit and my family for their endless support and Patrick, Caroline, Kachi, Foulques, for good times outside the laboratory.

Abstract

Myers has investigated pseudoephedrine as a highly selective chiral auxiliary for the alkylation of amide enolates. The aim of this project was to probe the currently accepted mechanistic rational of the pseudoephedrine amides as it is in dispute. The suggested mechanism is that the diastereolectivity is due to the pseudoephedrine alkoxide that blocks the 1*Si*,2*Re* face. However, a new hypothesis was put forward thanks to DFT calculations: it may be the aromatic ring that interacts with the enolate lithium cation which provides the shielding of that specific face. In order to probe this hypothesis a NMR investigation, including ^{1}H, ^{13}C, nOe signals, chemical shift measurements and *J* values, was carried out on the pseudoephedrine amide, the alkoxide and the enolate. Analysis of the latter was unsuccessful. However, the analysis on the pseudoephedrine amide and alkoxide show that these two compounds exist as two rotamers and are in an extended conformation differing only by the conformation of the α-proton with the *N*-methyl group. Moreover, two new pseudoephedrine derivatives with a fully reduced aromatic ring have been synthesised in two steps.

Abbreviations

FDA: Food and Drug Administration

TS: Transition state

P: Product

C: Compound

S: Substrate

de: Diastereomeric excess

ee: Enantiomeric excess

LDA: Lithium diisopropylamide

BuLi: *n*-Butyllithium

BnBr: Benzyl bromide

Boc_2O: Di-t*ert*-butoxycarbonyl

DCM: Dichloromethane

DFT: Density functional theory

DIBAL: Diisobutylaluminium hydride

Ph: Phenyl

Me: Methyl

t-Bu: *Tert*-butyl

Mg : Magnesium

HMPA: Hexamethylphosphoramide

NMR: Nuclear magnetic resonance

NOESY: Nuclear Overhauser effect spectroscopy

HOESY: Heteronuclear Overhauser effect spectroscopy

HSQC: Heteronuclear single-quantum correlation

HRMS: High resolution mass spectroscopy

IR: Infrared

S_Ni: Internal nucleophilic substitution

TEA: Triethylamine

THF: Tetrahydrofuran

TRIBAL: Triisobutylaluminium

LHMDS: Lithium bis(trimethylsilyl)amide

eq: Equivalent

rt: Room temperature

ppm: Parts per million

TLC: Thin layer chromatography

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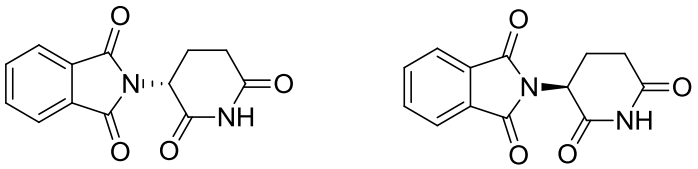
Chapter 1: Introduction

I. Asymmetric synthesis

Chirality plays an important role in our everyday life: from food ingredients such as aspartame, the commercial sweetener, to agrochemicals like pesticides and fungicides, to most known drugs.[1] Drugs and agrochemicals interact with biological systems that are comprised of non-racemic building blocks such as carbohydrates, amino acids and nucleic acids. The diastereomeric interaction between the biological target and the two enantiomeric forms of a drug or agrochemical are different and therefore results in a different biological response.[1-3] In the best case, the unwanted enantiomer is not bioactive and does not affect the activity of the drug. This would lead to a drug that is sold as a racemate. In the worst case, the unwanted enantiomer can inhibit the activity of the drug or even worse be toxic. Consequently, the unwanted enantiomer is considered an impurity and full toxicity tests must be run on each isomer for a drug to have FDA approval. The synthesis of a racemic mixture may lead to a waste of money, time and resources in the preparation of a mixture containing non-biologically active material. A well-known example of this would be the tragedy of thalidomide,[3] this drug was first put on the market as a racemic mixture in 1950 as a sedative to treat nausea of pregnant women.[4] Unfortunately the two enantiomers have different biological properties: the (*R*)-thalidomide **1a** is a sedative whereas the (*S*)-thalidomide **1b** (see **Figure 1**) is a teratogen that caused more than 10 000 deformed babies worldwide.[4] Therefore the drug was removed from the market in 1961.[4] This example illustrates the necessity to provide full testing while marketing a drug but also the necessity to further develop asymmetric synthesis.



(*R*)-thalidomide
1a

(*S*)-thalidomide
1b

Figure 1: Thalidomide enantiomers.

1. Definition

Asymmetric synthesis is defined as "a reaction or reaction sequence that selectively creates one configuration of one or more stereogenic elements by the action of a chiral reagent or auxiliary, acting on heterotopic faces, atoms, or groups of a substrate. The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate."[2]

In order to achieve an asymmetric synthesis it is necessary to understand how it occurs and why. In all the asymmetric approaches that will be discussed in the next chapter a chiral substrate or agent acts upon another chiral entity giving rise to diastereomeric transition states **TS**. The two different stereoisomers $\mathbf{P^1}$ and $\mathbf{P^2}$ in **Figure 2** , in their diastereomeric transition state ($[C^1\ldots S]^{\ddagger}$ or $[C^2\ldots S]^{\ddagger}$), differ in their free energy of activation $\Delta G^{\#}$ thus giving products at different rates.[5] Hence the greater the difference in free energy $\Delta\Delta G^{\#}$ between the two transition states the greater the selectivity: a difference of 2 kcal at 0 °C is considered necessary in order to provide one of the enantiomer with a 90:10 enantiomeric ratio.[6] This is what every chemist is looking to achieve: the highest selectivity possible.

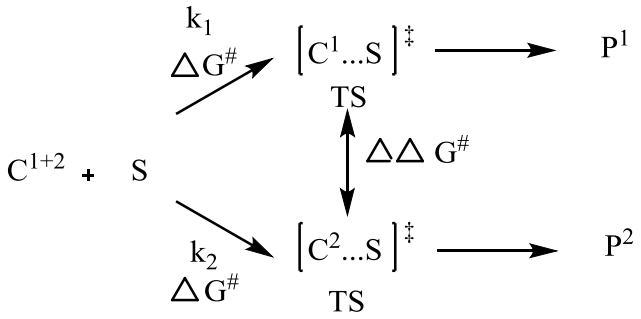


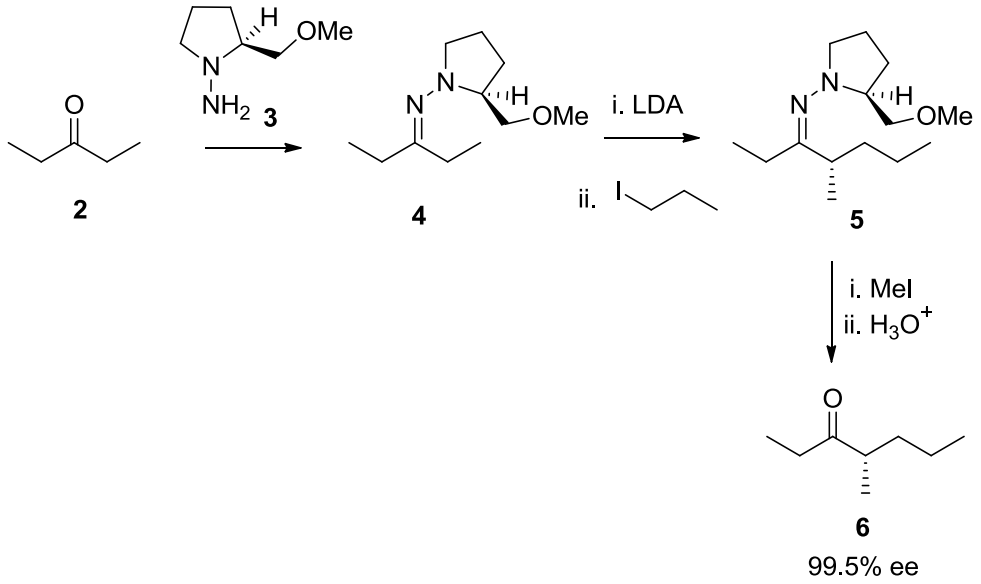
Figure 2: Diastereomeric transition states.

2. Approaches to asymmetric synthesis

There are four different approaches to asymmetric synthesis:

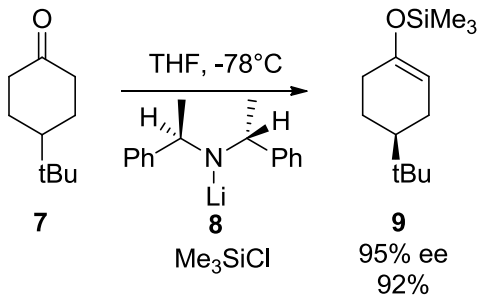
- The chiral pool: A chiron is an enantiomerically pure molecule already containing existing stereogenic units.[7] Normally the chiral pool is the source of the enantiomerically pure compound which is converted into the desired molecule. The chiral starting materials used can be amino acids, carbohydrates, hydroxyl acids, terpenes and sometimes alkaloids. This technique does not fit with the definition of asymmetric synthesis as the starting materials already have a stereogenic unit that directs the reaction.
- The auxiliary approach: This approach is similar to the chiron approach as the control is achieved by a chiral group within the substrate. Nonetheless it differs from it as the directing group, also called 'chiral auxiliary', is deliberately attached to the achiral starting material giving way to diastereoisomers after diasteresolective reactions with achiral reagents. These diastereoisomers can then be isolated as they have different physical properties and then the auxiliary can be easily removed in order to obtain the desired product in high ee.[3] For this type of approach, it is necessary to design a chiral auxiliary that will maximize the difference in free energy to obtain the highest selectivity. In order to do so, a rigid transition state with many contacts between the reacting partners by chelation, steric interactions, or hydrogen bonding is necessary.[8] An example of this would be the hydrazine SAMP **3** derived from (*S*)-proline developed by Enders and used

as an auxiliary for the alkylation of aldehydes and ketones, **Scheme 1**. The first step is the formation of the SAMP-hydrazone **4** from pentanone **2** followed by deprotonation and then attack on the alkyl halide to form **5**. The final step is the removal of the auxiliary resulting in the formation of ketone **6** with an excellent enantiomeric purity of 99.5% ee.[9]



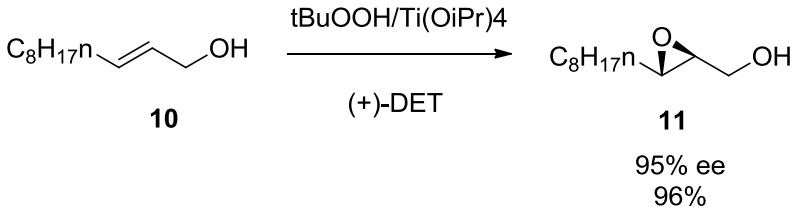
Scheme 1: Diastereomeric synthesis with SAMP as a chiral auxiliary.

- The chiral reagent approach: This technique distinguishes itself from the above as it uses a chiral reagent in order to obtain the desired selectivity. One example of a reaction using this approach is the asymmetric deprotonation of prochiral carbonyl compounds with a chiral base. The prochiral cyclohexanone **7** is deprotonated by the enantiomerically pure lithiated 1-phenylethylamine **8** which deprotonates selectively one of a pair of enaniotopic protons (see **Scheme 2**). The enolate is then trapped as the silyl enol ether **9** in good ee and yield.[3]



Scheme 2: **Selective deprotonation of ketone with a chiral base.**

- The chiral catalyst approach: The advantage of these 4th generation approaches is that they use a chiral catalyst in substoichiometric quantities. Accordingly it is more economical in terms of money but also in termsof synthetic efficiency: in one step with the correct chiral catalyst you can synthesise the product with the desired selectivity. A large range of reactions uses this approach: the Sharpless epoxidation of allylic alcohols is a good example. Here the allylic alcohol **10** in **Scheme 3** undergoes epoxidation with (+)-diethyl tartrate as the chiral ligand and titanium tetraisopropoxide and tert-butylhydroperoxide as the oxygen donor. The epoxide **11** is obtained in good yield and ee.[3]



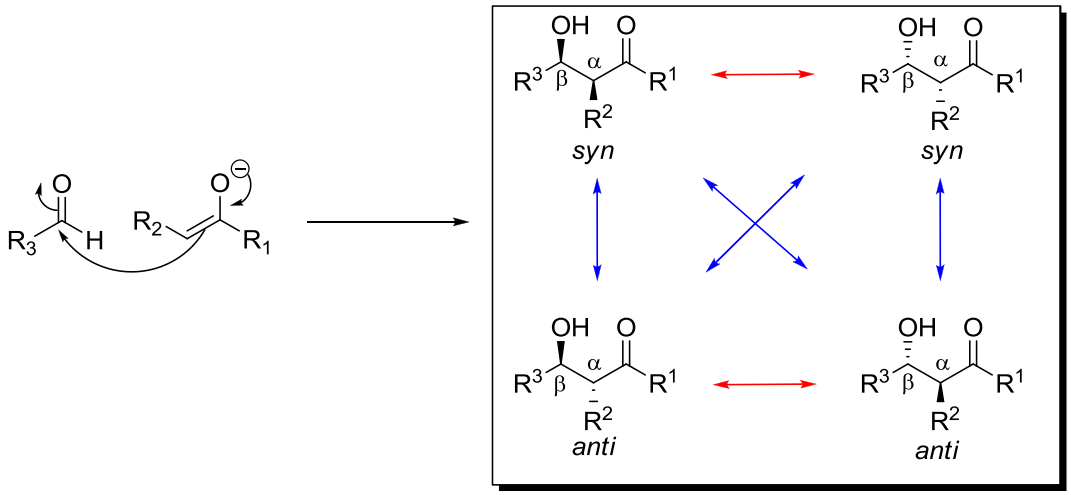
Scheme 3: **Diastereoselective epoxidation of an allylic alcohol.**

3. Chiral auxiliaries

This project is based on the stereoselective control obtained by using a chiral auxiliary. There are three major reactions based on this control: aldol, alkylation and Diels-Alder reactions. Only the first two reaction classes are relevant to this project will be discussed here.

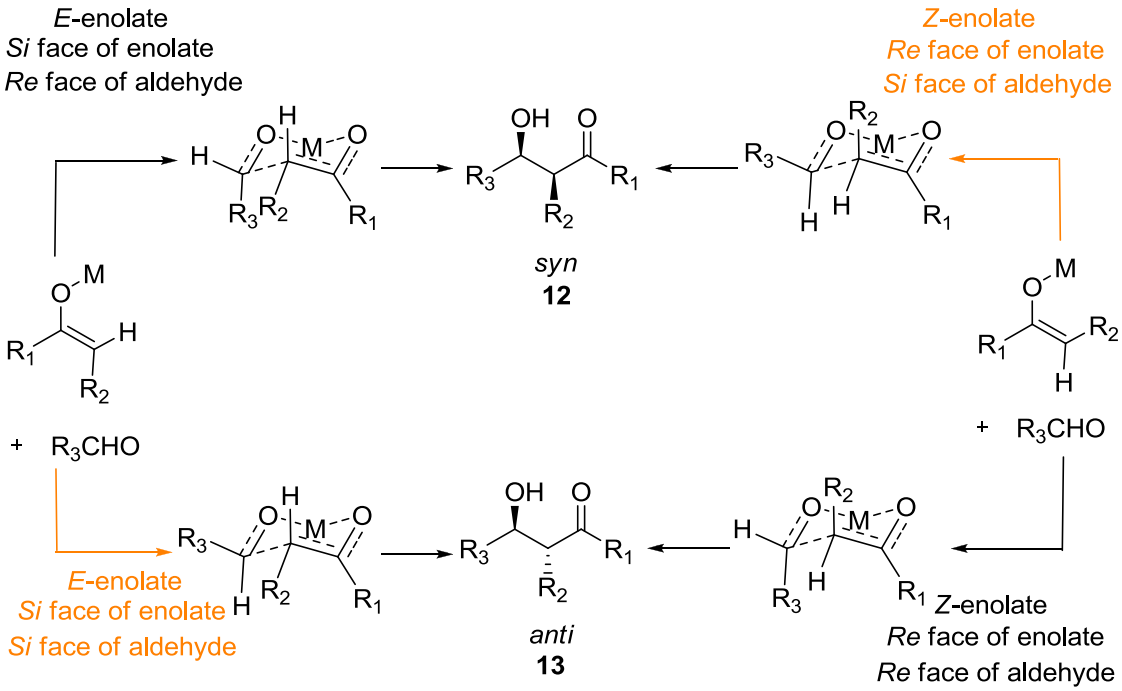
- Aldol

The aldol reaction between a nucleophilic carbonyl species with an electrophilic carbonyl moiety enables the formation of a new C-C bond and two new stereogenic centres in a single step.[5] It is possible to form four different stereoisomers that have an enantiomeric or diastereoisomeric relationship, **Scheme 4**.



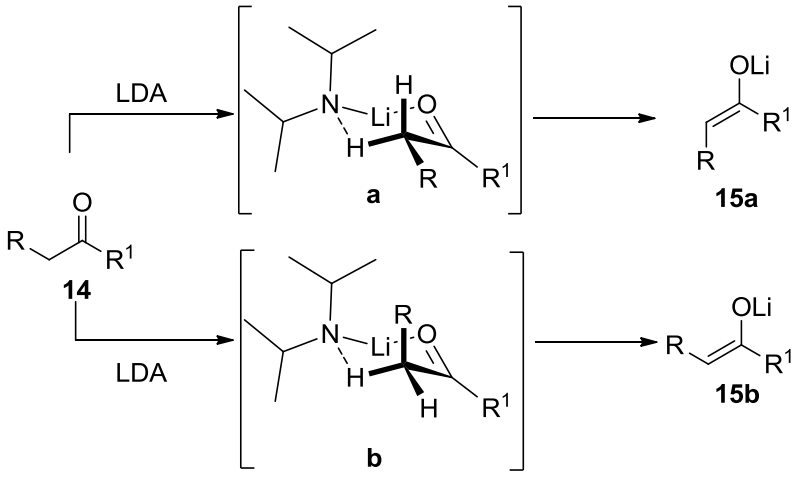
<u>Scheme 4:</u> Overview of the 4 diastereoisomers susceptible to form in an aldol reaction.

The *syn*/*anti* outcome of the α and β carbons can be predicted from the Zimmerman-Traxler model which is based on a six membered ring transition state. This model also depends on the geometry of the enolate: *Z* and *E*, **Scheme 5**.[5]



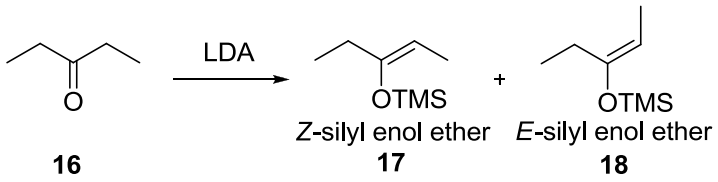
Scheme 5: Mechanistic rational according to the configuration of the enolate.

The *Z*-enolate can approach the aldehyde from the *Si* face giving the *syn* product **12** or the *Re* face giving the *anti* product **13**. Nevertheless, this model shows that when the *Z*-enolate approaches the aldehyde by the *Si* face, and the R^1 and R^3 are moderately large, there is a 1,3-diaxial interaction which disfavours the *anti* outcome. In a similar way, the *E*-enolate can also approach the *Re* face giving the *syn* product **12** or the *Si* face giving the *anti* product **13** which is favoured for the same reasons. Therefore in order to control the stereochemical outcome, the geometry of the enolate must be controlled which is linked to the base used and the substituent on C^1 of the enolate. If LDA is used for example as the base for deprotonation of the carbonyl **14** the process can undergo two possible pathways leading to the *Z*-enolate **15b** or the *E*-enolate **15a**, **Scheme 6**.



Scheme 6: Configuration adopted according to the substituents of the ketone by deprotonation with LDA.

In kinetic enolization of carbonyl compounds, the larger the R^1 group in **14** the more *Z*-enolate **15b** is formed due to less steric hindrance between R^1 and a proton than R and R^1 during the transition state **a** or **b** of the protonation process.[10,11] Moreover the solvent also influences the stereochemical outcome as stipulated by Ireland.[12] He examined the influence of solvent on the deprotonation the symmetrical ketone 3-pentanone **16** with LDA in THF and with or without HMPA, **Scheme 7**.

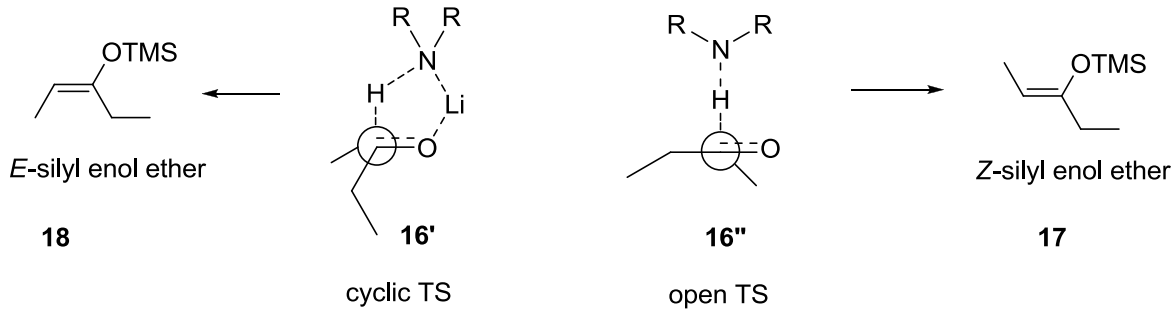


Scheme 7: Deprotonation of 3-pentanone 16.

	Solvent	Z/E ratio
1	THF	23/77
2	THF/HMPA (23 vol % HMPA-THF)	95/5

Table 1: ***Z*/*E*** **outcome of enolate formation according to the conditions used.**[12]

As seen in **Table 1**, a high degree of selectivity is obtained according to the conditions used. In the presence of THF, the *E*-silyl enol ether **18** was preferably obtained in a 77/23 ratio (**Table 1 entry 1**). When the deprotonation occurs in THF/HMPA the *Z*-silyl enol ether **17** was obtained with a higher selectivity of 95/5 (**Table 1 entry 2**). This selectivity resides in the kinetic enolization of the ketone and the influence of the solvent used on this enolization.



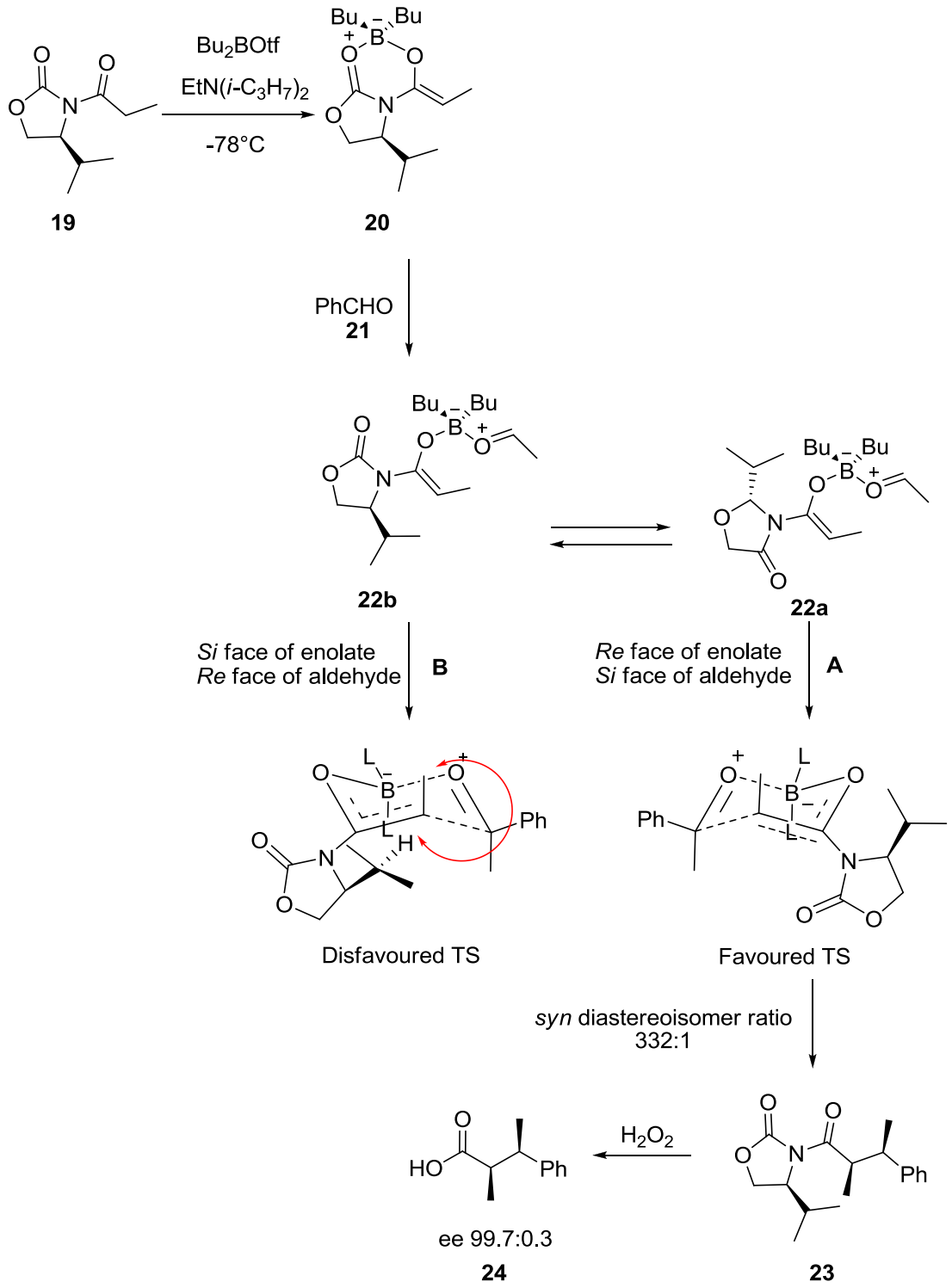
Scheme 8: **TS of the enolate.**

As THF is a less coordinating solvent, there is a strong interaction of the Li^+ cation with the carbonyl oxygen resulting in a cyclic transition state **16'** leading to the *E*-silyl enol ether **18** see **Scheme 8**. In contrast, HMPA solvates the Li^+ cation resulting in an open TS **16"** to give the *Z*-silyl enol ether **17**.[12]

Therefore, the solvent used will also influence the stereochemical outcome as well as the reaction conditions and the use of chiral auxiliaries.[5] Furthermore, all that

applies for the enolate formation and diastereoselectivity outcome also applies for azaenolates and amide enolates as well.

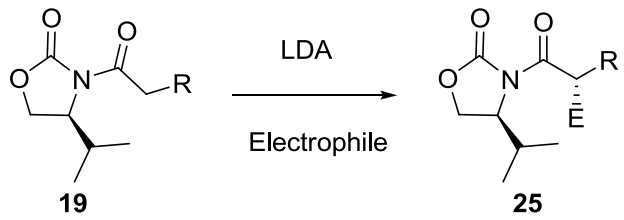
A well-known example of chiral auxiliaries are the Evans' oxazolidinones which have played an important role in aldol and alkylation reactions by forming an amide enolate during the process. In **Scheme 9**, the *Z*-enolate **22b** is exclusively formed by using dibutylboron triflate with the amide **19** and Hünig's base for deprotonation. The boron coordinates to the two oxygen atoms providing the rigid transition state **20**. Before the aldol reaction takes place the boron needs to coordinate with the oxygen from the aldehyde **21** in order to activate it. As the boron can only coordinate to two oxygen atoms it no longer chelates from the carbonyl of the oxazolidinone. This leads to the possibility of two rotamers **22a** and **22b** that can react with the aldehyde **21**: enolate **22a** can react with its *Re* face onto the *Si* face of the aldehyde (pathway A) or enolate **22b** can react with its *Si* face onto the *Re* face of the aldehyde (pathway B). Nevertheless, there is a steric repulsion between the methyl group of the enolate and the isopropyl group of the chiral auxiliary for **22b**. This leads to a full *syn* diastereomeric outcome of the aldol reaction to obtain **23**; the auxiliary is then removed to afford the carboxylic acid **24** with a high ee.[8,13]



<u>Scheme 9:</u> Diastereoselective aldol reaction by using Evans' chiral auxiliary.

- Alkylation

Evans' oxazolidinones can also be used in diastereoselective alkylation reactions employing the enolate to react with an electrophile.[14] **Scheme 10**.



Scheme 10: Diastereoselective alkylation with Evans' chiral auxiliary and an electrophile.

	R	Electrophile	Crude de	Isolated yield
1	Me	$PhCH_2Br$	<99:1	92%
2	Me	$CH_2=CHCH_2Br$	98:2	71%
3	Me	EtI	94:6	36%
4	Et	MeI	89:11	79%

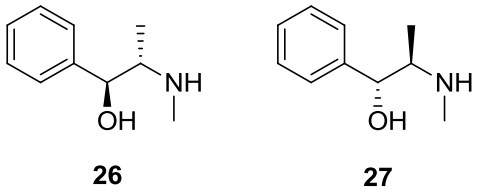
Table 2: Diastereoselective excess and yield according to the electrophile used.

LDA deprotonates the amide **19** to form exclusively the *Z*-enolate which then reacts with activated electrophiles such as a benzyl or allyl halide to form **25** in high yield and with excellent diastereoselectivity **Table 2** entry **1** and **2**. Unfortunately, with unreactive halides there is a loss in selectivity and yield as seen in **Table 2 entries 3** and **4**.[14]

Diastereoselective alkylation can be achieved by the use of a range of chiral auxiliaries such as Evans' oxazolidinones described above[14] or camphor sultams used by Oppolzer.[15] Nevertheless, Evans oxazolidinones react poorly with unactivated alkyl halides while camphor sultam require the use of carcinogenic

HMPA. Therefore in 1994, Myers seized the opportunity to use pseudoephedrine as a chiral auxiliary in the asymmetric alkylation of carboxamides with a high diastereoselectivity.[16,17]

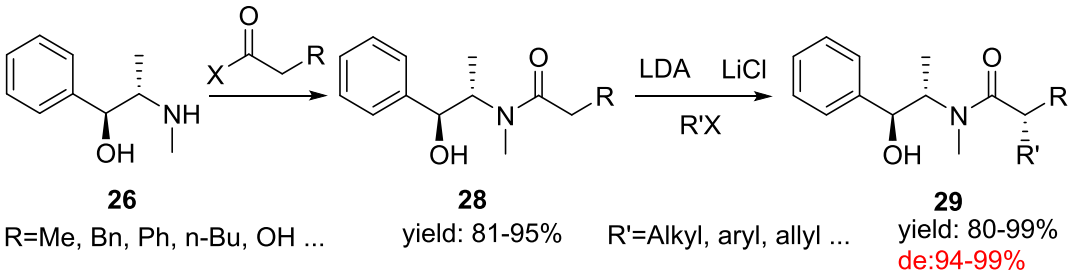
Pseudoephedrine **26** or **27** is a biologically active compound used as a nasal decongestant and stimulant which is produced routinely with a worldwide annual production of 300 metric tons.[16] Both enantiomers can be accessed easily and cheaply: (1*S*,2*S*) **26** and (1*R*,2*R*) **27**, **Figure 3**.



26 **27**

Figure 3: The two enantiomers of pseudoephedrine.

Myers' work allowed access to a wide range of compounds by viable alkylation with unreactive halides, something that was not previously available with oxazolidinones especially with non-activated alkyl halides. Alkylation of pseudoephedrine amide enolates (e.g. derived from **28**) gave good yield, good diastereomeric excesses and was relatively straightforward.[17] **Scheme 11**.



Scheme 11: Alkylation of pseudoephedrine amides.

The next step was to find a plausible mechanism to understand the high diastereoselectivity observed. Pseudoephedrine amides (e.g. **28**) are structurally similar to prolinol amides. Askin *et al.* suggested that the alkoxy group from the prolinol amide enolate directed the alkylation as it provided a steric shielding **30**.[18]

Hence, Myers suggested a similar argument to explain the selectivity and proposed the following conformation **28'** shown in **Figure 4**.

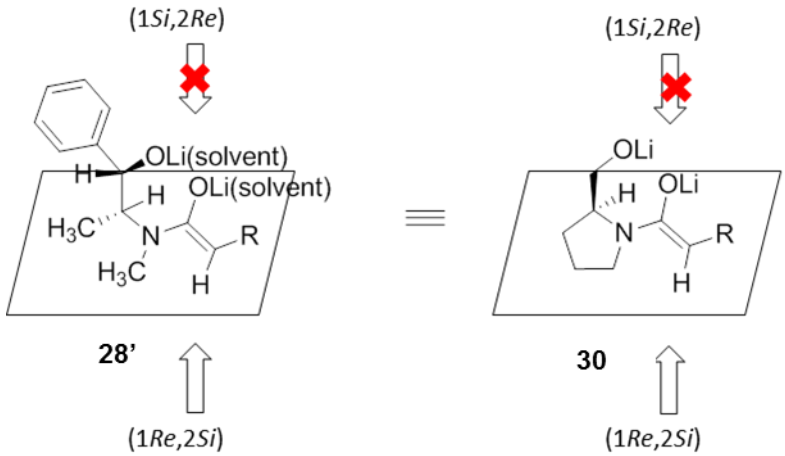


Figure 4: Suggested conformation by Myers inspired by Askin.[17]

The pseudoephedrine amide *Z*-enolate **28'** adopts a staggered conformation where the lithium alkoxide and the solvent molecules are proposed to block the 1*Si*,2*Re* face forcing the attack on the electrophile by the 1*Re*,2*Si* face. Myers suggested this staggered conformation as a result of an X-ray structure of pseudoephedrine glycinamide hydrate **31** in which a similar conformation was observed.[17] **Figure 5**.

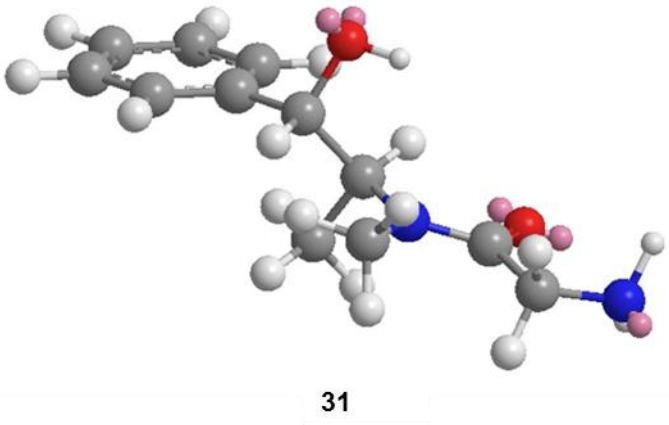
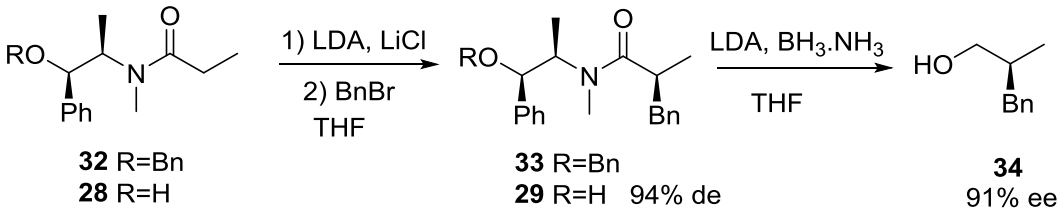


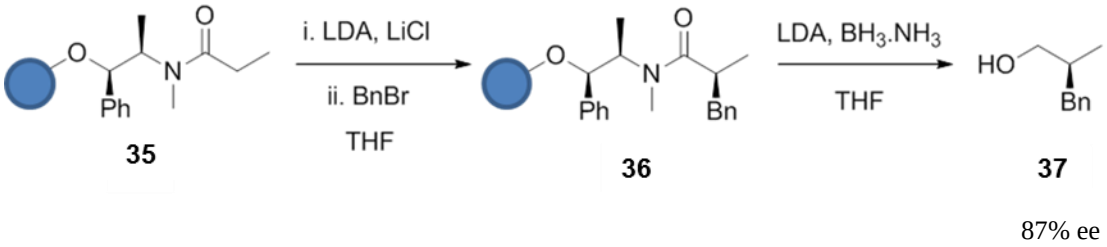
Figure 5: Chem3D Pro representation of the X-ray structure of pseudoephedrine glycinamide hydrate.[17]

In 2003, Procter evaluated pseudoephedrine as a linker for asymmetric alkylation on a solid support.[19] First of all, he had to ensure that high diastereoselectivity would still be observed in alkylating the *O*-benzylpseudoephedrine amide **32** as the pseudoephedrine alkoxy group would be linked to the resin, so the formation of a dianion would be impossible. Fortunately, the synthesis afforded an ee of 91% of **34** which is comparable to the de of 94% obtained for the alkylation of pseudoephedrine amide **28**.[19] **Scheme 12**.



Scheme 12: Alkylation of *O*-benzylpseudoephedrine amide 32.

The same conditions were applied to the *O*-polymer-supported pseudoephedrine amide **35** by deprotonation followed by alkylation to give **36** which then undergoes deprotection to obtain **37** with 87% ee[19] see **Scheme 13**. Therefore, linking pseudoephedrine amide **28** to a resin through oxygen did not greatly affect the diastereomeric ratio.



Scheme 13: Diastereoselective alkylation of *O*-polymer-supported pseudoephedrine amide.

The oxygen from the *O*-polymer-supported pseudoephedrine **35** might not be able to coordinate to the lithium due to the steric bulk of the polymer attachment and therefore may not lie over the enolate face as **28'**. This work implies that the

conformation of the dianion **28'** proposed by Myers is not essential for good facial selectivity.

With these results in mind, Gibson performed computational work in order to determine the lowest energy conformation of the pseudoephedrine amide enolate by single point calculation using DFT B3LYP with the 6-31G** basis set of the molecular mechanics derived conformations (ca 90 conformations).[20] This analysis revealed that Myers conformation **28'** was not the lowest energy conformer; an interaction between the lithium cation from the enolate and the aromatic ring gave the lowest energy **28''**. **Figure 6**.

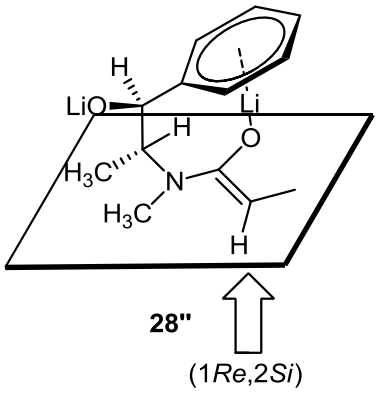


Figure 6: New mechanistic hypothesis: π-Li interaction.

This conformation led to a new hypothesis: The aromatic ring provides the steric shielding of the 1*Si*, 2*Re* face. Consequently, by enhancing the electron density of the ring this should tighten the interaction between the ring and the lithium cation and enhance the facial selectivity and *vice versa*.

In order to prove this hypothesis, the synthesis of pseudoephedrine analogues with electron rich and electron poor aromatic groups must be carried out. If the hypothesis is revealed plausible, a loss in the diastereomeric excess with electron poor aromatic groups may be observed and an enhancement in diastereomeric ratio with electron rich aromatic groups will be observed. The following pseudoephedrine amide analogues that have been selected will then be subjected to the alkylation protocol. **Figure 7**.

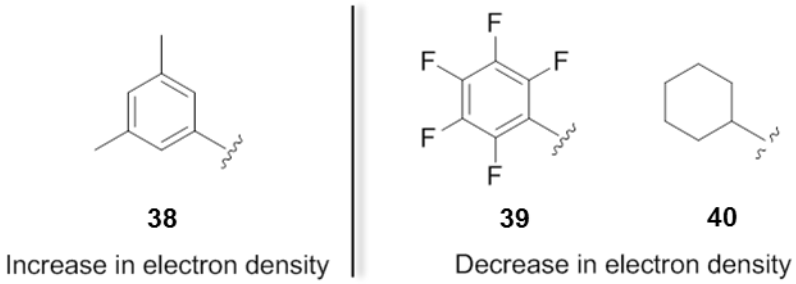


Figure 7: Analogues of pseudoephedrine amides.

On the other hand, if Myers' low energy conformation is the correct reactive species then there ought to be no loss in diastereoselectivity according to the electron deficient or electron rich analogues used. The aim of this project was to synthesise the electron poor analogues **39** and **40** in order to prove this hypothesis.

II. NMR studies

Another means of proving the hypothesis was to undertake NMR studies such as ^{1}H, ^{13}C and NOESY experiments. The nuclear Overhauser effect is used to establish correlations through space between nuclear spins of protons and not through bonds. If there is a nOe signal between two protons then they are less than 5 Å away. This experiment helps in determining the conformation of a molecule[21] and therefore might be of use regarding the conformation of the enolate forming during the alkylation.

In this case, the calculated structures indicate that the enolate Li is more than 4.06 Å from the aromatic protons and unlikely to be seen by $^{6}Li[^{1}H]$ HOESY for both conformations.[20] Therefore, it was required to use NOESY in order to determine which conformation is the most accurate. Gibson, with molecular modeling, was able to predict the distances for both conformation **28'** (**Figure 8**) and **28''** (**Figure 9**).[20]

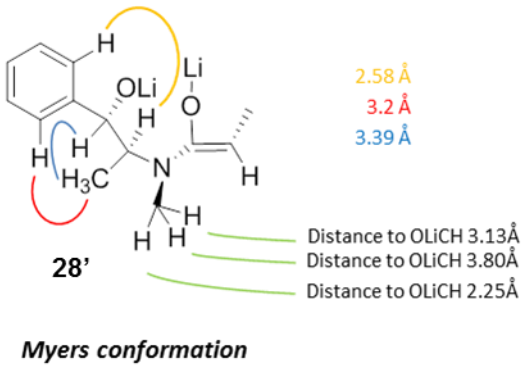


Figure 8: Predicted nOe cross signals for Myers conformation of enolate 28'.

By NOESY it might not be possible to see all these correlations even though they are less than 5 Å a part. It is considered that signals for the protons that are less than 3.2 Å away may be observed in both cases. If **28'** is the ground state conformation then the protons correlations in yellow and red should give a nOe correlation as well as the protons from the *N*-Me with OCHLi may be seen (**Figure 8**). As for the alternative conformation **28"**, fewer signals are predicted to be detected: only the yellow and red labeled proton interactions. **Figure 9**.

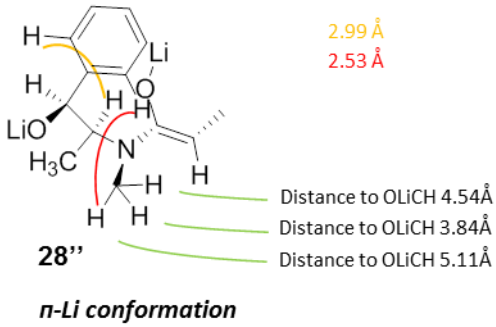
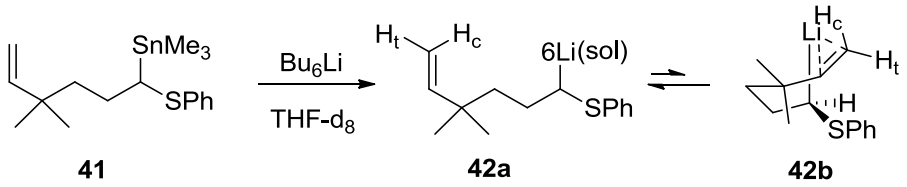


Figure 9: Predicted nOe cross signals for the π-Li conformation.

Therefore, according to the signals seen on the NOESY data, the conformation of the pseudoephedrine enolate might be determined.

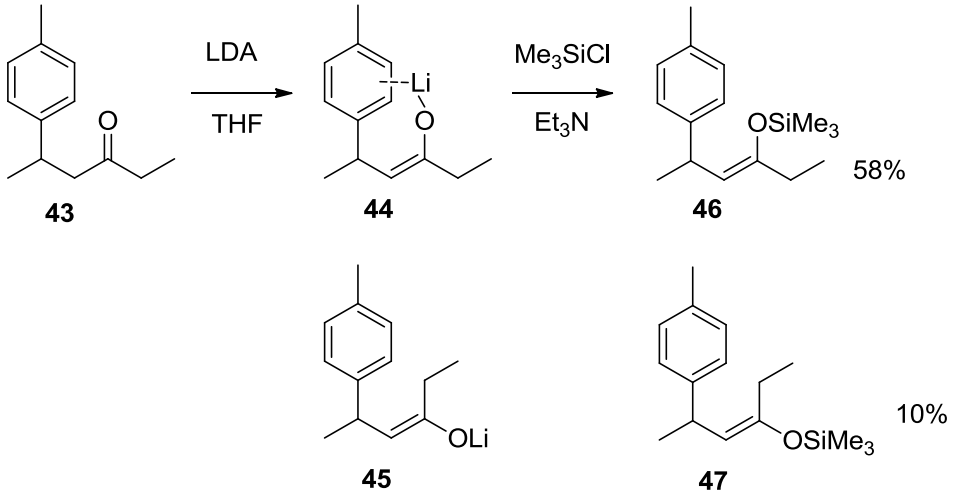
Moreover, ^{13}C might also be of use in this case as it has been studied by Hoffman to show that π-Li interaction can affect the chemical shift of carbons.[22] In this work, they studied the lithiation of **41** and discovered that the hexenyllithium **42** exists as two distinct species in solution **42a**, the 'normal' alkyllithium and **42b**, the

complexed π-Li species in a ratio of 5.5:1 (**Scheme 14**). The two species **42a** and **42b** show no difference in chemical shift for the protons H_c and H_t. However they differ in the chemical shifts of the alkenyl carbon atoms with **42a** δ= 109.2 and 150.8 ppm and **42b** δ= 111.3 and 148 ppm.[22]



Scheme 14: Study of the two species of hexenyllithium.[22]

Posner and co-workers also carried out a study on the influence of π-Li coordination on the regiochemistry of the lithiation of unsymmetrical ketones bearing a neighbouring aromatic group. These workers noticed that lithiation of 5-tolyl-3-hexanone **43** gave rise to a 6:1 mixture of two lithium enolates: *Z* **44** and *E* **45 (**ratio established by producing the enol silyl ethers **46** and **47**, respectively) see **Scheme 15**. The NMR studies on these enolates **46** and **47** revealed that the C_α of the *E*-enolate **45** showed a normal chemical shift for a lithium enolate at 102.3ppm whereas the *Z*-enolate **44** with the lithium-π interaction, the enolate C_α shifted upfield at 98.5ppm. This difference in chemical shift indicates that there is more electron density at the C_α in the π-Li intermediate.[23]



Scheme 15: Study of the influence of π-Li interaction on the chemical shifts of the C_{α}.[23]

Therefore, Gibson carried out a 6-31G** single point calculation[20] to determine how the carbons from the aromatic ring might differ in chemical shifts according to the conformation of the pseudeoephedrine enolate **48**. **Table 3** reveals that carbons A, B and C from **48** (**Figure 10**) differ in chemical shifts significantly if the Myers conformation **28'** or the π-Li conformation **28''** is observed.

	A	**B**	**D**
Amide OLi 28a 2 conformers	152.8 155.3	**129.5** 120.9	126.5 125.5
Z-enolate 28b with π-Li interaction 28''	**157.8**	**134**	**123.5**
Z-enolate 28b Myers 28'	**154.4**	**129**	**125.8**

Table 3: Chemical shifts of the aromatic carbons of pseudoephedrine enolate 28b and alkoxy 28a

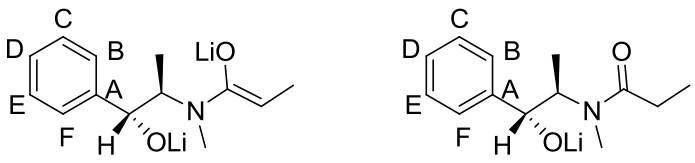


Figure 10: Pseudoephedrine enolate 28b and pseudoephedrine alkoxy 28a.

Consequently, it was decided to investigate by NMR analysis the amide **28**, the alkoxide **28a** and the enolate **28b** (**Figure 11**). For each of them, ^{1}H NMR, ^{13}C NMR, and NOESY were to be carried out in order to determine which major ground state conformation the enolate adopts.

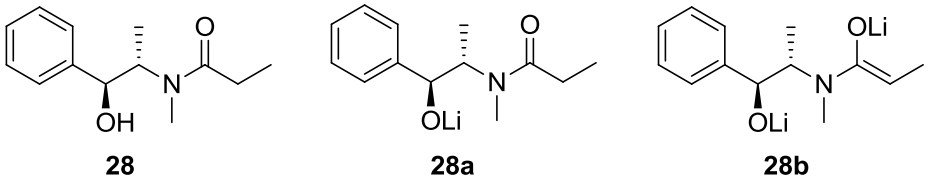
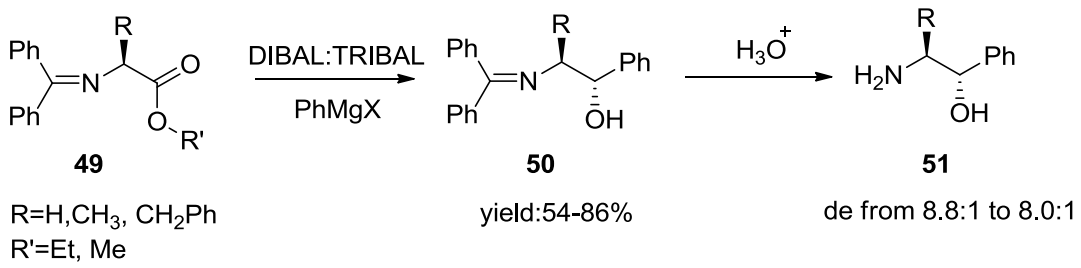


Figure 11: The three compounds submitted to NMR analysis.

III. Proposed synthetic route

The most important step of synthesising the proposed electron deficient analogues was obtaining the chiral alcohol e.g. **51**. Polt *et al.* studied the reaction of imine-protected amino esters **49** with an aluminium hydride source followed by alkylation with a Grignard reagent. Subsequent cleavage of the Schiff base **50** provided the *threo*-2-amino alcohols **51** in high yield and good *syn* selectivity.[24] **Scheme 16**.



49 **50** **51**

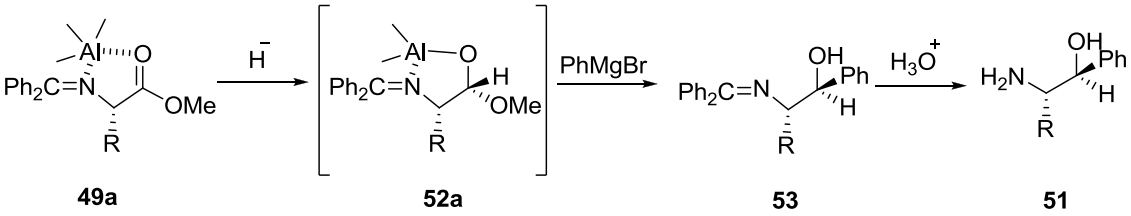
R=H,CH_3, CH_2Ph
R'=Et, Me

yield:54-86%

de from 8.8:1 to 8.0:1

Scheme 16: Diastereoselective reductive alkylation of imine protected amino esters 49.

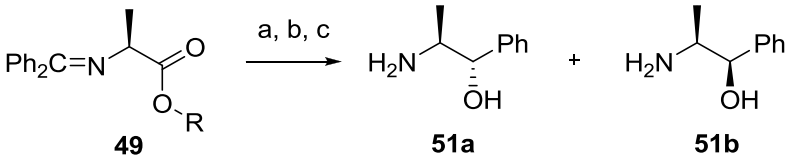
In order to obtain **49** before the alkylative reduction, Polt and co-workers converted the corresponding amino acid into an ester and then this was treated with benzophenone imine to obtain **49** and its derivatives. The treatment of **49** at -78 °C with a 1:1 diisobutylaluminum hydride and triisobutylaluminum solution in hexane delivered the hydride source on the *Re* face and enabled the complex **52a** to form (**Scheme 17**). This complex was treated with a nucleophile that attacked the less hindered face and displaced the methoxy group to obtain **53** which was then hydrolysed to form **51** with a good ee.[24]



49a **52a** **53** **51**

Scheme 87: Mechanistic rational for the reductive alkylation of 49 in Et_2O.

Polt *et al.* have also determined that the hydride transfer was the stereochemically significant step in this reaction. The tight complex **49a** formed with the aluminium hydride reagent provides a source of chelation and blocks the *Si* face of the ester. Moreover, Polt's group decided to study the impact of the ester group with reference to its steric bulk as well as the solvent on the stereochemical outcome of the reductive alkylation (**Scheme 18** and **Table 4**).[24]



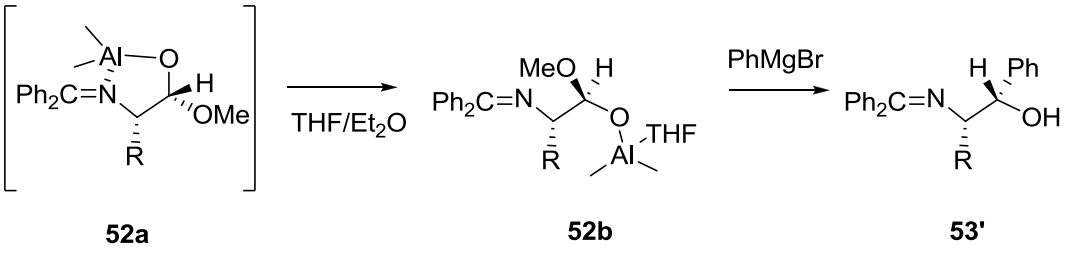
a. 1 eq of DIBAL:TRIBAL in DCM at -78 °C
b. 3 eq of PhMgBr in Et_2O or in Et_2O/THF at -78 °C to 0 °C
c. H_3O^+

Scheme 98: Study of the impact of solvents on the diastereoselective outcome of the reductive alkylation of alanine derivatives 49.

	Ester	**51a/51b** In Et_2O	**51a/51b** In Et_2O/THF
1	**49a** R'=Me	7.6:1	2.7:1
2	**49b** R'=Et	8.8:1	2.6:1
3	**49c** R'=*t*-Bu	11:1	3.8:1

Table 4: Diastereoselective excess of the reductive alkylation to provide alcohol 51a/b according to the solvent used and substituents on the ether.

As seen in **Table 4**, the bulkier the ester group, the more selective the reductive alkylation. In this context, the *tert*-butyl ester **49c** gave an 11:1 selectivity in favour of the 1*S*,2*S* compound **51a** in diethyl ether (**Table 4 entry 3**). When THF was used in diethyl ether, which is a more polar solvent, a loss in selectivity was observed with a 3.8:1 selectivity for the 1*S*,2*S* compound **51a** using the *tert*-butyl ester **49c** (**Table 4 entry 3**). This can be explained by the chelate ring of the initial complex **52a** being opened by THF and therefore providing a higher percentage of the minor non-chelated aluminoxy acetal **52b** to be attacked by the Grignard to afford **53'** (see **Scheme 19)**.[24]

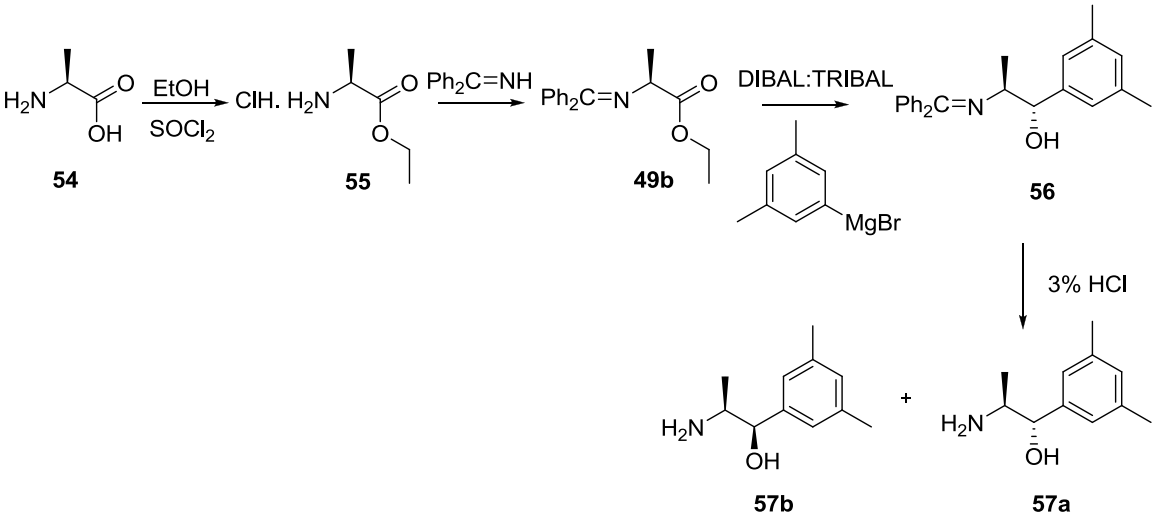


52a **52b** **53'**

Scheme 19: **Mechanistic rationale of the reductive alkylation of 49 in the presence of THF.**

Moreover due to the polarity of THF this can increase the rate of alkoxide elimination favouring a S_N1-like pathway.[24] It is, therefore, necessary to use less polar solvents and bulkier ester alkyl groups to favour the 1*S*,2*S* compound.

In our laboratories, Coti initially used the synthetic approach of Polt and co-workers in the reductive alkylation by starting with L-alanine **54** in order to obtain the norephedrine analogue **57a** (**Scheme 20**).[25]



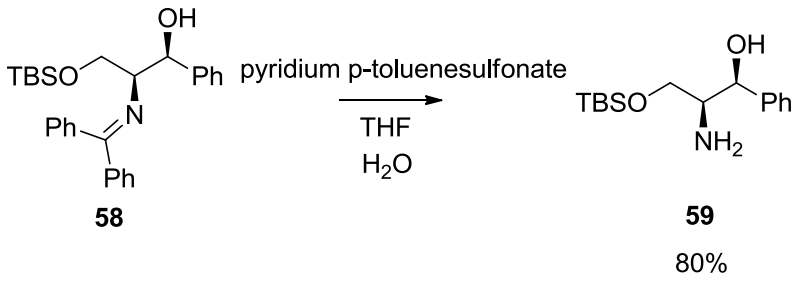
54 **55** **49b** **56** **57b** **57a**

Scheme 20: **Coti's synthetic approach to pseudoephedrine analogues.**

After the formation of the amino-alcohol **56** from the ester **49b**, the ketimine group was removed with acid. Unfortunately Coti reported that the cleavage of the ketimine group of **56** resulted in epimerization of the hydroxyl group giving both **57a** and **57b** which did not occur for Polt.[24] Coti tried different reaction conditions using HCl or citric acid, however none of these approaches avoided the

epimerization problems.[25] This is possibly a result of the increased lability of the C-1 position of **56** through increased electron density from the more electron rich aryl ring.

In subsequent work, Polt *et al.* deprotected the ketimine group in **58** by using pyridium *p*-toluenesulfonate in THF which gave **59** in good yield (**Scheme 21**).[26]

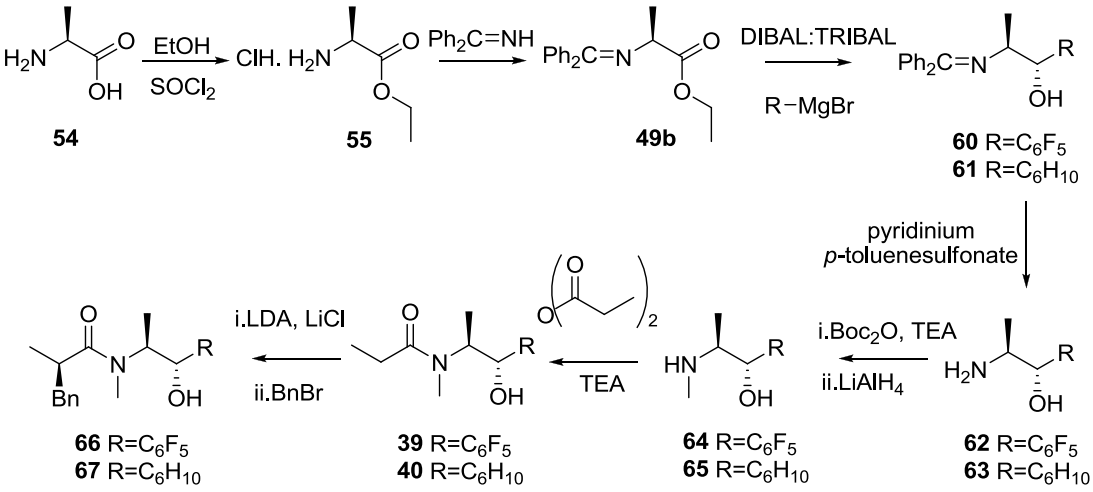


58 **59**

80%

Scheme 21: Deprotection of the ketimine group.

In this work it was proposed that the preparation of pseudoephedrine amide derivatives with electron deficient aromatic rings (**Scheme 22**) would be undertaken. The use of pyridium *p*-toluenesulfonate in THF in the deprotection step may be an alternative approach to avoid possible epimerization.



54 **55** **49b**

60 R=C_6F_5
61 R=C_6H_{10}

66 R=C_6F_5
67 R=C_6H_{10}

39 R=C_6F_5
40 R=C_6H_{10}

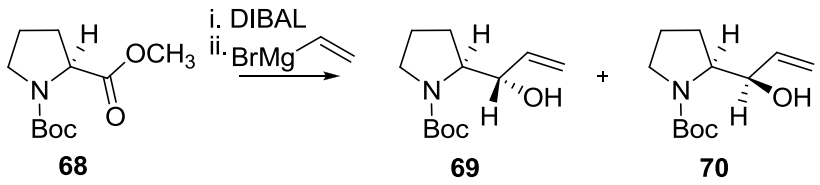
64 R=C_6F_5
65 R=C_6H_{10}

62 R=C_6F_5
63 R=C_6H_{10}

Scheme 22: New synthetic approach for electron poor derivatives of pseudoephedrine amide.

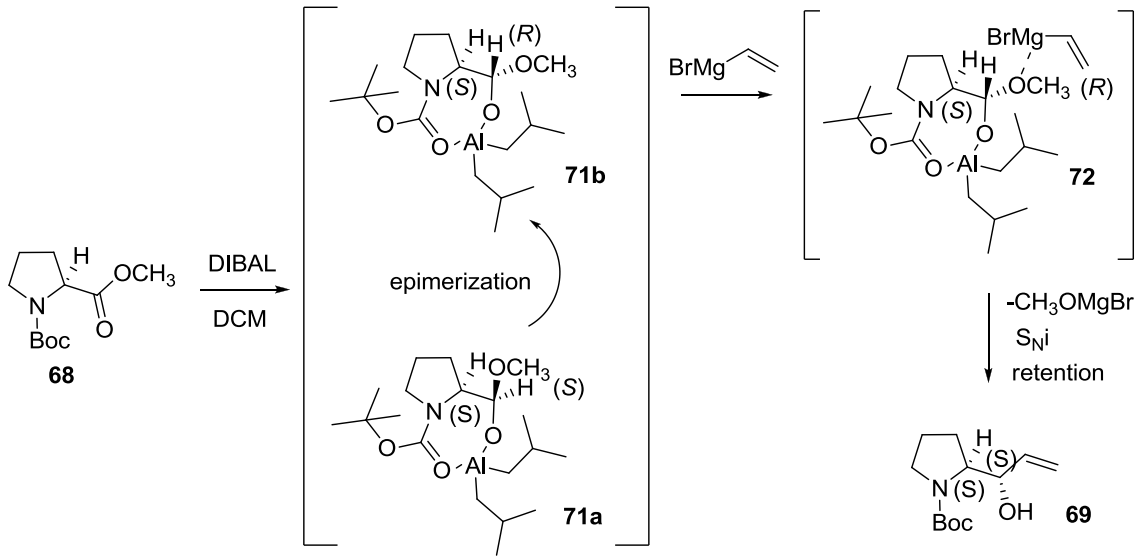
Therefore, the new synthetic approach, inspired by Coti[25] starts with the synthesis of the amino ester hydrochloride salt **55** by treating the amino acid **54** with thionyl chloride and ethanol. It will be followed with the protection of the amine as a Schiff's base **49b** with benzophenone imine. The reductive alkylation of **49b** with different Grignard reagents will lead to the two alcohols **60** and **61** which will then be deprotected with pyridinium *p*-toluenesulfonate to have amino alcohols **62** and **63**. The next step consisted of *N*-methylation by Boc protecting and then reducing to obtain amino alcohols **64** and **65** which will then be *N*-acylated with propionic anhydride and triethyl amine. The pseudoephedrine analogs **39** and **40** will then be alkylated with Myers conditions.[17]

Coti revised the synthetic route to pseudoephedrine amide analogues **38**, **39** or **40** based on observations made by Zhao *et al*.[27] Zhao performed a reductive alkylation on Boc L-proline methyl ester **68** with DIBAL and a Grignard reagent to obtain the allylic alcohol **69** with high selectivity.[27] (**Scheme 23**)



<u>Scheme 23:</u> Zhao's synthetic approach by reductive alkylation to from allylic alcohols 69 and 70.

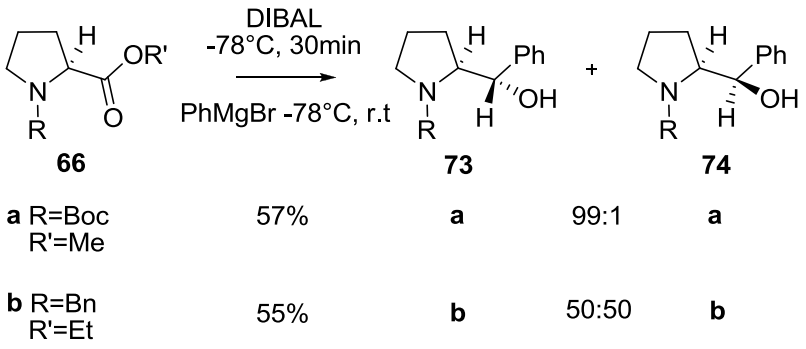
Zhao varied a number of parameters in the reductive alkylation of ester **68**. The highest yield of 69% was obtained with a high selectivity of 32:1 in favour of the *S*,*S* isomer **69**.[27] This was achieved by warming up the reaction mixture to -20 °C after the addition of the DIBAL at -78 °C. The subsequent addition of the Grignard reagent was performed at -78 °C. These conditions were crucial for high selectivity. It was believed that the reaction proceeds through a 7-member ring chelated intermediate **71** formed by the chelation of the aluminium with the oxygen of the Boc and the oxygen from the carbonyl of the ester,[27] **Scheme 24**.



Scheme 24: Mechanistic rational for the selectivity observed.

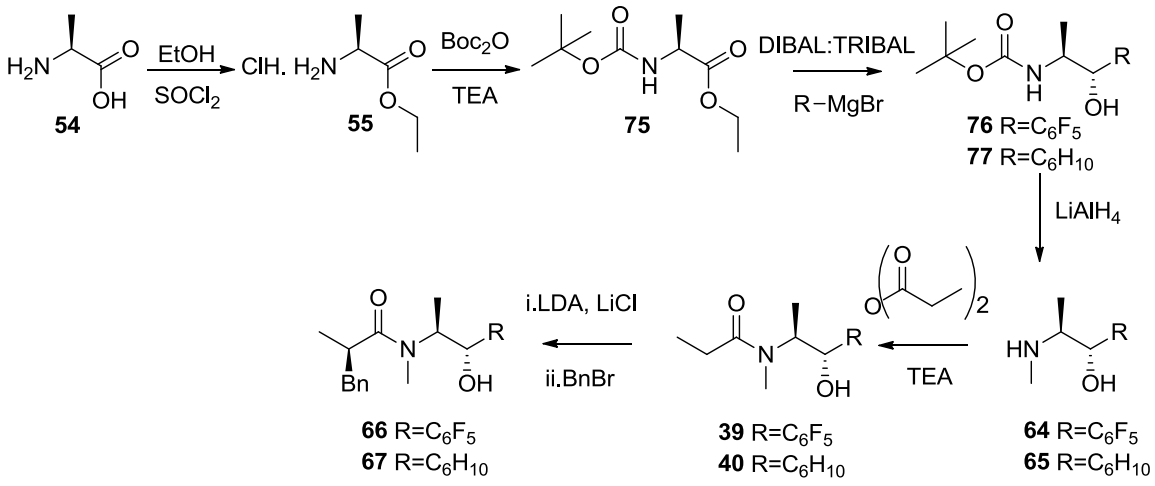
Zhao suggested that the DIBAL reduction of ester **68** generates the major diastereomer **71a**. Epimerization of **71a** occurs during the warm step to -20 °C to lead to the intermediate **71b** which is sterically less hindered than **71a**. Then the Grignard reagent displaces the methoxy group through a S_Ni type mechanism to provide (*S*,*S*) allylic alcohol **69** in good yield and high selectivity.[27] Zhao also investigated the use of a Lewis acid like zinc chloride instead of the warm up step. This also gave good selectivity and yield for the generation of the alcohol **69** without a lengthy warm up step. Unfortunately it is not known yet how this influences the epimerization of **71a** to **71b**.[27]

This technique was also extended to the use of phenylmagnesium bromide with proline derivatives **66a** and **66b** by Cochi *et al*.[28]



Scheme 25: Reductive alkylation with phenyl magnesium bromide.

As seen in **Scheme 25**, good selectivity was obtained for the Boc protected proline ester **73a** with a diastereomeric ratio of 99:1. In contrast, when the *N*-benzyl proline ester **66b** was submitted to the same conditions a 1:1 diastereomeric ratio of **73b** and **74b** was obtained.[28] The Boc group was, therefore, necessary in order to obtain high diastereoselectivity; this was explained by the 7-member ring intermediate **71** mentioned previously. It was, therefore, decided to use the following synthetic route to obtain the pseudoephedrine amide analogues **39** and **40** see **Scheme 26**.



Scheme 26: Boc protected synthesis route to obtain the alkylated electron poor peusodephedrine amide analogues 66 and 67.

Consequently, the new synthetic approach started with the synthesis of the amino ester hydrochloride salt **55** by treating the amino acid **54** with thionyl chloride and ethanol. The amine was then protected to obtain the Boc derivative **75** which was

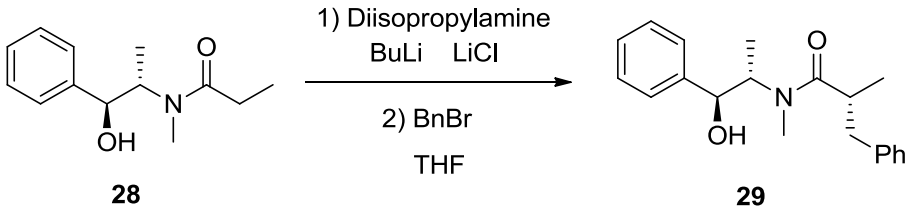
then subjected to reductive alkylation with different Grignard reagents to afford two alcohols **76** and **77**. The Boc group was then to be reduced to give the *N*-methylated alcohols **64** and **65**, followed by *N*-acylation with propionic anhydride and triethyl amine. The pseudoephedrine analogs **39** and **40** obtained were then to be alkylated under Myers conditions.[17]

In summary, Myers has suggested using pseudoephedrine amide e.g. **28** as a chiral auxiliary for asymmetric alkylation which gave good yields and excellent diastereoselectivity in the asymmetric alkylation. His mechanistic rationale was questioned when *O*-benzyl and *O*-polymer supported pseudoephedrine amide where shown by Procter and co-workers to still give good diastereoselectivities of alkylated products. Therefore, based on DFT calculations, a new hypothesis was suggested involving a π-Li interaction instead of the alkoxy blocking the 1*Si*,2*Re* face of the pseudoephedrine amide enolate. In order to probe the likelihood of these mechanistic suggestions it was proposed to synthesize pseudoephedrine amide analogues varying the electron density of the aromatic ring (e.g. **39** and **40** in **Scheme 26**). These derivatives would then be submitted to the same amide alkylation conditions used by Myers in order to determine which transition state is more plausible according to the selectivity observed. Moreover, a NMR study was to be carried out in parallel on the amide **28**, alkoxide **28a** and enolate **28b** in order to see the possible ground state conformation the amide enolates **28'** or **28"** adopt during the alkylation.

Chapter 2: Results & Discussion

I. Alkylation of pseudoephedrine amide

Prior to the proposed NMR experiments, it was important to understand and master Myers' alkylation reaction[16,17] of pseudoephedrine amides e.g. **28** in order to see if similar yields could be obtained. **Scheme 27**.



Scheme 27: Alkylation of pseudoephedrine amide 28 with BnBr.

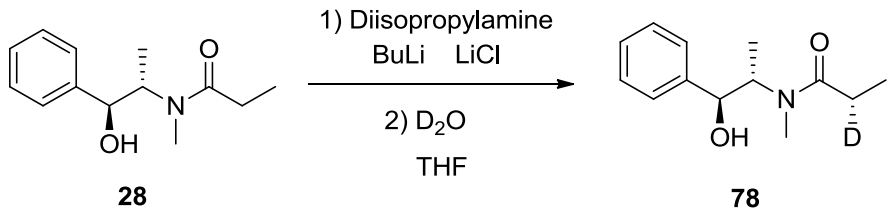
The formation of the base was carried out at -78 °C where *n*-BuLi was added to diisopropylamine in anhydrous THF followed by a brief stirring a 0 °C. The amide **28** in anhydrous THF at 0 °C was then added to the base and left to stir for 1 hour at -78 °C then 15 minutes at 0 °C, 5 minutes at room temperature. The resulting solution was then finally brought back down to 0 °C for the addition of benzyl bromide to give alkylated product **29**. This reaction is sensitive to water and air implying that glassware must be dry and the reaction must be under an inert atmosphere. Several attempts were tried by varying the reaction conditions **Table 5.** The first set of conditions did not yield any product as the amide was not dried. Therefore, the next reaction was attempted with dried amide (**entry 2**) and then again by distilling the alkyl halide from calcium hydride (**entry 3**). Unfortunately no alkylated product was isolated which was thought to be because the lithium diisopropylamide was not forming. Hence, the *n*-BuLi was titrated and it was revealed that the concentration was of 1.44 M instead of 2.5 M as the bottle indicated. The titration of *n*-BuLi consists by adding drop by drop the base in a stirred solution of diphenylacetic acid in dry THF until the solution becomes yellow (see Experimental section).[29]

Moreover, one must be sure that the reaction is at -78 °C before the addition of *n*-BuLi as above -35 °C, *n*-BuLi can open the THF ring.[30] With that in mind, the next attempt was carried out with 4 equivalents of diisopropylamine and 4 equivalents the titrated *n*-BuLi. The latter was added 30 minutes after the solution was brought down to -78 °C, in order to make sure that the lithiated base was formed. The recovery of only 5% of product was insufficient and warranted further investigation.

	mmol amide **28** (drying method)	LiCl 6 eq.	Diisopro-pylamine 2.25 eq.	BuLi 2.08 eq.	BnBr 1.5 eq.	Time before BnBr addition	Yield **29**
1	0.452	dried at 150 °C		2.5 M		1 h at -78 °C 15 min at 0 °C 5 min at rt	-
2	0.637 (drying pistol at 2 mbar at 40 °C)	drying pistol at 150 °C		2.5 M		same	-
3	0.673 **(**drying pistol at 2 mbar)	drying pistol at 150 °C		2.5 M	distilled	same	-
4	0.678 (dried with $CaCO_3$ and azeotropic removal with toluene)	flame dried	4 eq.	4 eq. 1.44 M	distilled	same	5%

Table 5: Different conditions applied to the alkylation of pseudoephedrine amide 28.

Therefore, it was decided that the enolate of **28** would be quenched by deuterium oxide leading to an exchange of a proton with deuterium as seen in **Scheme 28**. This exchange can easily be seen by proton NMR. This would help to identify if the problem was the formation of the enolate or the alkylation.



Scheme 28: Alkylation of pseudoephedrine amide 28 with D_2O.

	mmol amide **28** (drying method)	LiCl 6 eq.	Diisopro-pylamine 2.25 eq.	BuLi 2.08 eq.	Time before D_2O addition	Yield **78**
1	0.565 (dried with $CaCO_3$ and azeotropic removal with toluene + drying pistol at 2 mbar)	drying pistol at 2 mbar at 150 °C + flame dried		1.44 M	1 h at -78 °C 15 min at 0 °C 5 min at rt	-
2	0.452 (dried with $CaCO_3$ and azeotropic removal with toluene + drying pistol at 2 mbar at 40 °C)	drying pistol at 2 mbar at 150 °C + flame dried		2.5 M new bottle	same	50%

Table 6: Different conditions to obtain the deuterated product 78.

After recovering no deuteriated product **78** with the first attempt (**Table 6 entry 1**), it was noticed that *n*-BuLi when used was a grey solution. A new bottle of *n*-BuLi was therefore bought and 50% of **78** was recovered (**entry 2**) indicating that the enolate was forming.

	mmol amide **28** (drying method)	LiCl 6 eq.	Diisopro-pylamine 2.25 eq.	BuLi 2.1 eq.	BnBr 1.5 eq.	Time before BnBr addition	Yield **29**
1	0.316 (dried with $CaCO_3$ and azeotropic removal with toluene + drying pistol at 2 mbar)	dried at 140 °C + flame dried		2.5 M	distilled	1 h at -78 °C 30 min at 0 °C 15 min at rt	10%
2	0.565 (drying pistol at 2 mbar)	dried at 140 °C + flame dried	distilled	1.88 M	distilled	same	52%
3	0.633 (drying pistol at 2 mbar)	dried at 140 °C + flame dried	distilled	1.88 M	distilled	1 h at -78 °C 1 h at 0 °C 40 min at rt	71%

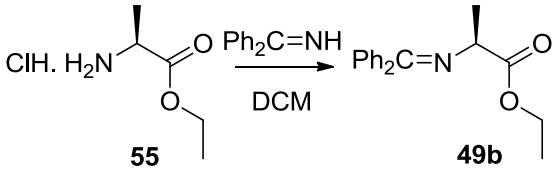
Table 7: Different conditions applied to the alkylation of pseudoephedrine amide 28.

With the previous results in hand, it was possible to alkylate **28** with BnBr to give **29** in 10% yield (**Table 7 entry 1**). This led us to believe that the diisopropylamine should be distilled in order to ensure that no traces of water were present. It was also decided that the new bottle of *n*-BuLi should be titrated[29] also: the concentration was 1.88 M. This shows that even if a new bottle is bought titration is necessary regarding *n*-BuLi. The alkylation reaction was consequently carried out with every reagent dried by distillation or drying pistol (2 mbar) and with a known concentration of *n*-BuLi which gave a 52% yield (**Table 7 entry 2**). The results were encouraging and it was thought that a longer exposure time to form the enolate would be needed before the addition of BnBr. It was possible to isolate 71% of **29** (**Table 7 entry 3**) by letting the enolate form for 1 hour at -78 °C then 1 hour at 0 °C and finally 40 minutes at room temperature upon addition of the alkyl halide at 0 °C. Purification by flash chromatography did not give any problems. It was also possible to isolate the alkylated amide **29** by recrystallization with hot toluene.

II. Synthesis of the cylcohexyl amide pseudoephedrine analogue **40**

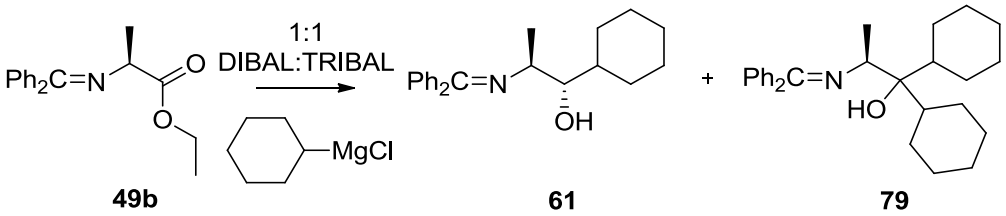
1. Ketimine route

This route was inspired by Polt *et al.* and the synthesis of pseudonorephedrine [24] as mentioned earlier (Chapter 1, III). The first step consisted of synthesizing the ketimine protected alanine ester **49b**. (**Scheme 29**)



Scheme 29: Synthesis of the ketimine protected ester.

The amino hydrochloride salt **55** in DCM was reacted with benzophenone imine according to O'Donnell's protocol.[31] This gave the enantiomerically pure ketimine alanine ester **49b** upon recrystallization in cold hexane in 80%. The next step was to reduce and alkylate the alanine ester **49b** by modifying Polt's conditions (**Scheme 30**).[24]

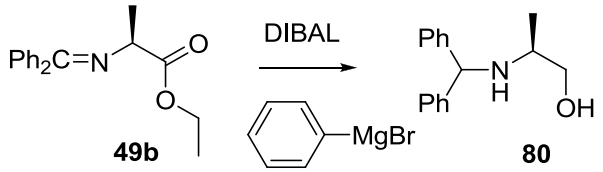


Scheme 30: Reductive alkylation of ketimine 49b.

	mmol of **49b** (drying method)	Cyclohexylmagnesium chloride	Time before Grignard addition	Yield **61**	Yield **79**
1	0.355 (drying pistol at 2 mbar)	2 M one shot addition	-	-	70%
2	0.355 (drying pistol at 2 mbar)	2 M drop wise addition	3h	-	93%
3	0.409 (drying pistol at 2 mbar)	2 M drop wise addition	5h	-	44%

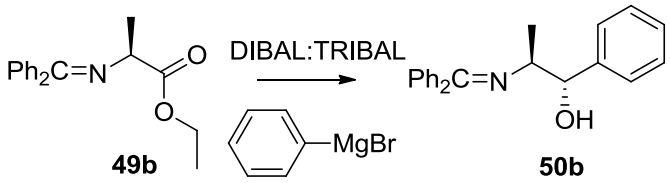
Table 8: Conditions used for the reductive alkylation of 49b.

The first attempt was carried out according to Polt's protocol[24] which consisted of adding the prepared 1:1 reducing solution DIBAL:TRIBAL at -78 °C followed by the addition of the Grignard reagent in Et_2O in one charge. This resulted in a 70% yield of the dialkylated product **79** (**Table 8 entry 1**). It was thought that this might be due to the fact that the DIBAL:TRIBAL intermediate did not have time to form. Therefore, in the next attempt the reduction was left for 3 hours at -78 °C before the addition of the Grignard reagent (**Table 8 entry 2**) and after that 5 hours (**Table 8 entry 3**). In both cases, only the dialkylated product **76** was recovered. Hence, these results implied that the DIBAL was not reducing the ester and it was thought that the hydride was not at the concentration indicated on the bottle as previously seen with *n*-BuLi. The titration of DIBAL according to Hoye[32] revealed a concentration of 0.66 M instead of 1 M. This technique consists in adding DIBAL to a stirred solution of *p*-anisaldehyde in anhydrous ether at 0 °C followed by the addition of glacial acetic acid. An aliquot was then transferred to a NMR tube and a no-D NMR was carried out. With the conversion of the aldehyde into an alcohol we were able to determine the concentration of the reducing agent.[32]



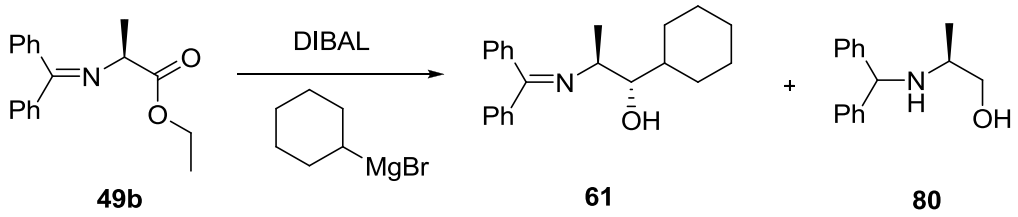
Scheme 31: Reduction of ketamine 49b.[24]

With the determination of the actual concentration of the reducing agent, it was important to know if the ester **49b** was being reduced by the DIBAL by using 2 equivalents of the reducing agent. The starting material **49b** in anhydrous DCM was added drop wise to a DIBAL solution in DCM at -78 °C which was then left to stir for 4 hours (**Scheme 31**). The Grignard reagent PhMgBr in ether at 2 M was then added and left to stir overnight to give 21% of over reduced product **80**. The reaction was tried again but this time by using the same equivalents and addition order as Polt[24] and using PhMgBr. In the hands of Polt and co-workers the alcohol ketimine **50b** had been synthesized in 78% yield (**Scheme 32**).[24]



Scheme 1032: Reductive alkylation of 49b with Polt's conditions.[24]

The ester **49b** was reduced by the addition of a 1:1 solution of DIBAL:TRIBAL at -78 °C. The complex was left to form for 5 hours before addition of the Grignard reagent at -78 °C and left to stir overnight at room temperature. Amino alcohol **50b** was isolated with 28% yield. The same conditions were applied to the ester **49b** but with cyclohexylmagnesium chloride (commercially available) this time which gave an 18% yield of **61**. Zhao's conditions [27] with the ketimine protecting group were also attempted (**Scheme 33**).



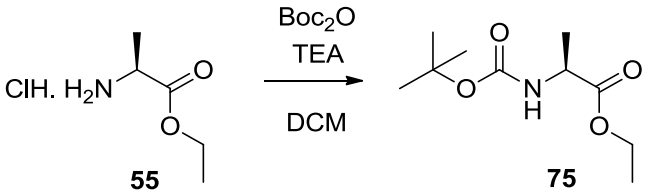
Scheme 33: Reductive alkylation of 49b using Zhao's conditions.[27]

Therefore, 2 equivalents of DIBAL were added to the ester **49b** in THF at -78 °C and left to stir for 3 hours (**Scheme 33**). Then the solution was warmed up to -20 °C for 1 hour and brought back down to -78 °C for the drop-wise addition of the freshly prepared cyclohexylmagnesium bromide (details of this given in Chapter 2, I, 2). Purification of the crude product by flash chromatography gave several fractions. Analysis of these fractions by NMR was carried out and unfortunately none of them gave the same proton NMR as the previously formed product **61**. We were only able to isolate the over reduced product **80** in 27 % yield.

This reductive alkylation step with Polt's conditions gave low yields which could have been expected. The cyclohexylmagnesium halide is sterically more demanding than aromatic or allyl metal nucleophiles. Therefore, we decided to synthesize the pseudoephedrine amide derivative **40** via the Boc route described below.

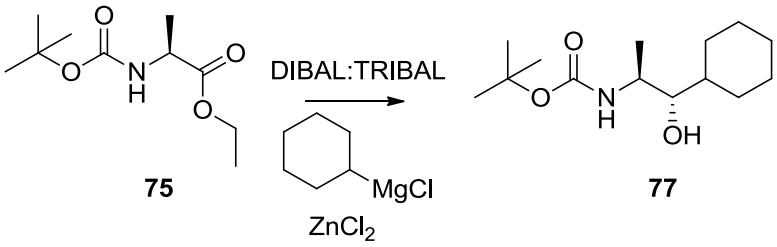
2. The Boc route

As the ketimine route did not provide us with good results, the Boc route was investigated as mentioned in Chapter 1, II.



Scheme 34: Boc protection of 55.

The first step went smoothly by treating the hydrochloride salt **55** with triethylamine to give the free the amine which then reacted with di-*tert*-butyl dicarbonate which gave the Boc protected ester **75** in 91% yield after purification (**Scheme 34**). The next step was to form the amino alcohol **77** by reductive alkylation (**Scheme 35**).



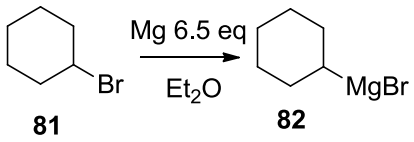
Scheme 35: Reductive alkylation of 75.

	mmol **75** (drying method)	Conc. of DIBAL/ TRIBAL	$ZnCl_2$	Grignard	Time	Yield **77**
1	1.105 **(**drying pistol at 2 mbar)	0.66 M/1 M	-	2 M drop wise addition	5 h before Grignard addition	14%
2	1.266 (drying pistol at 2 mbar)	0.69 M/1 M	0.1 eq. @ 1 M	2 M drop wise addition	2 h before $ZnCl_2$ 3 h before Grignard addition	16%

Table 9: Different conditions used for the reductive alkylation of 75.

The reaction conditions are similar to those of the ketimine protected ester **49b** for the first attempt with a 5 hour formation of the intermediate. With these conditions, the amino alcohol **77** was isolated in 14% yield (**Table 9 entry 1**) as a mixture of diastereoisomers. The diastereomeric ratio is close to 1:1 which implies no selectivity whatsoever. It was decided herein to apply Zhao's conditions[27] in order to improve the diastereoselective outcome by using $ZnCl_2$ to enhance the epimerization.[27] Therefore, the ester **75** in anhydrous DCM at -78 °C was reduced by a 1:1 solution of DIBAL-TRIBAL and left to stir for 2 hours. Then the Lewis acid $ZnCl_2$ in solvent, in catalytic amount, was added and the reaction left to stir for another 3 hours in order for the intermediate to epimerize completely. Finally the

cyclohexylmagnesium chloride was added drop-wise to the solution. After purification, **77** was obtained with a better diastereomeric excess of 2:1 in 16% yield (**Table 9 entry 2**). After these results it was valuable to investigate the use of freshly prepared Grignard **82** (**Scheme 36**).



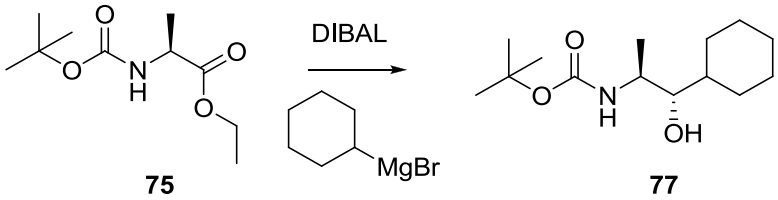
Scheme 36: Grignard synthesis of 82.

	Mg	Cyclohexyl bromide	Concentration	Conversion
1	4.7 g	3.7 mL (1.26 mmol)	0.34 M	7%
2	15.8 g	12.3 mL (5 mmol)	0.41 M	25%

Table 10: Conditions used for the formation of the Grignard 82.

Baker *et al.* reported that in order to enhance the formation of Grignard reagents the magnesium turnings had to be activated by sonication or by simply stirring vigorously the turnings under inert atmosphere.[33] Therefore, in each case the magnesium turnings were flame dried and left to stir under inert atmosphere overnight. A thin layer of black powder could be observed the following day on the side of the flask. Then the magnesium turnings were covered with dry diethyl ether. The two entries differ by the way the addition of the freshly distilled cyclohexyl bromide was added. For the first attempt the halide was added drop-wise to a solution stirred normally and kept under reflux for 2 hours. This solution was titrated according to Hoye[34] and had a concentration of 0.34 M giving a 7% conversion (**Table 10 entry 1**). The titration method consists of adding a known volume of Grignard to a known amount of an external standard like cyclooctadiene. A NMR was then used to determine the concentration (see Experimental section).[34] This conversion proved to be deceptive as we were expecting a better conversion. Baker

also reported that in order to have a better conversion the freshly distilled halide should be added drop-wise in the vortex of the solution.[33] This was carried out for the second attempt and gave a better conversion of 25% with a concentration of 0.41 M (**Table 10 entry 2**). As this provided sufficient amount of the Grignard for the reductive alkylation step improvements in the conversion were not investigated.



Scheme 37: Reductive alkylation of 75 using Zhao's conditions.[27]

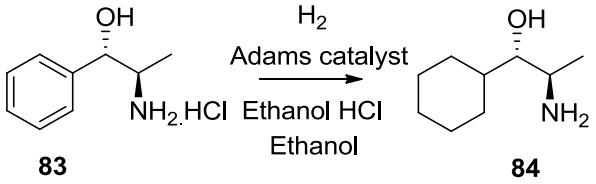
The last attempt in the reductive alkylation of the ester **75** (**Scheme 37**) was carried out by reducing ester **75** at -78 °C with only DIBAL and leaving the intermediate to form for 3 hours. Then the reaction was warmed up to -20 °C for 1 hour in order for the epimerization of the intermediate to proceed. The solution was brought back down to -78 °C before the addition of the freshly prepared Grignard reagent at 0.41 M. The first purification (15-50% ethyl acetate/85-50% hexane) gave a mixture of diastereoisomers 3:1 in favour of the desired diastereoisomer (400 mg, 33%). Further purification by chromatography was undertaken (10% ethyl acetate/90% hexane) to isolate the desired diastereoisomer **77** (80 mg, 6% yield) as well as a mixture of diastereoisomers (250 mg) 3:1 in favour of the desired diastereoisomer.

In summary, the isolation of the desired diastereoisomer has not been easy. We were unable to isolate enough **77** and the reaction conditions were a challenge. A new route was looked into in order to isolate pseudoephedrine amide analogue **40** in a decent yield and easily accessible.

3. New route

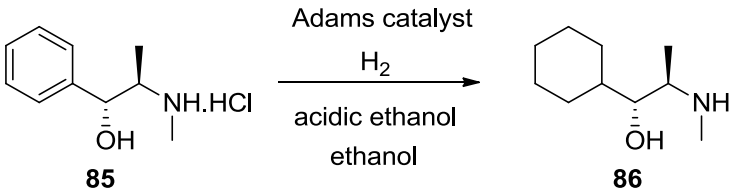
Due to the low yields and low diastereoselectivity in the reductive alkylation of **49** and **75** with cyclohexylmagnesium halides, it was decided to change route and have

a more direct route to the cyclohexyl pseudoephedrine amide analogue **40**. This was inspired by a Czech group led by Sicher who looked into hydrogenating norephedrine hydrochloride **83** which gave the hexahydronorephedrine **84** in 91% yield (**Scheme 38**).[35]



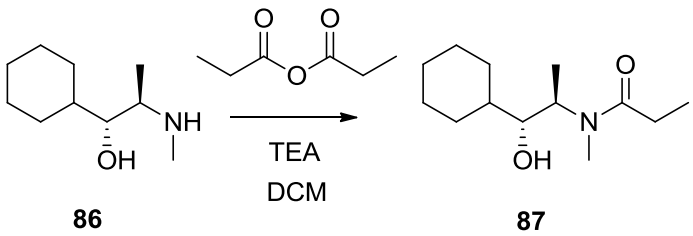
Scheme 38: Hydrogenation of norepehedrine.

This protocol could therefore be tested on (1*S*,2*S*)-pseudoephedrine to obtain (1*S*,2*S*)-hexahydropseudoephedrine. The pseudoephedrine isomers e.g. **85** are restricted materials, however, a sample of (1*R*,2*R*)-pseudoephedrine was available for use.



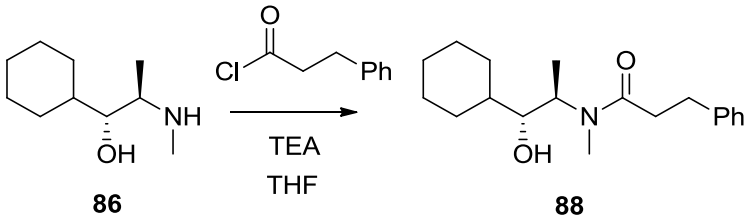
Scheme 39: Hydrogenation of pseudoephedrine hydrochloride 85.

Therefore the synthesis was carried out using (1*R*,2*R*)-pseudoephedrine hydrochloride **85** in the presence of Adams catalyst and hydrogen (**Scheme 39**). The reaction went smoothly and afforded the hexahydropseudoephedrine **86** in 71%.



Scheme 40: *N*-acylation of pseudoephedrine 86.

The amine **86** was then treated with triethylamine and propionic anhydride in anhydrous DCM to form hexahydropseudoephedrine amide **87** in 47% yield (**Scheme 40**). In order to fully understand the alkylation reaction and moreover the two diastereoisomers that can derive from that reaction an additional amide **88** was synthesized.



86 **88**

Scheme 41: ***N*-acylation of pseudoephedrine 86.**

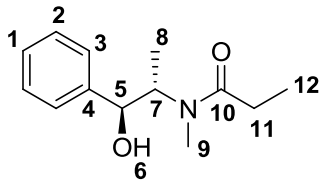
The amine **86** was dissolved in anhydrous THF whereupon triethylamine was added and then hydrocinnamoyl chloride (**Scheme 41**). The amide **88** was isolated in 17% yield. Both of these amide synthesis were carried out according to Myers protocol.[17]

In summary the reductive alkylation of the Schiff base **49b** did not give us very good yields as well as with the Boc protected amino ester **75**. This step revealed to be long and challenging leading us to look into another route by reduction of pseudoephedrine hydrochloride salt **85**. We were able to isolate both cyclohexyl pseudoephedrine amide analogues **87** and **88** by *N*-acylation with propionic anhydride and hydrocinnamoyl chloride and triethyl amine. However time constraints did not allow us to alkylate them under Myers' conditions.

III. NMR studies

The conformational study on the pseudoephedrine amide **28**, the alkoxide **28a** and the enolate **28b** was to be carried out thanks to ^{1}H, ^{13}C and NOESY experiments. The results might indicate which conformation the enolate adopts: Myers configuration **28'** or the π-Li interaction configuration **28''**.

1. Pseudoephedrine amide **28**



28

Figure 11: Pseudoephedrine amide 28.

Pseudoephedrine amide **28** (**Figure 11**) was subjected to an extensive NMR study in dried tetrahydrofuran d_8. A variety of NMR experiments of the amide **28** were investigated including ^{1}H, ^{13}C, HSQC and NOESY were carried out on the amide.

Amide **28** Carbon No.	^{1}H chemical shifts in ppm		^{13}C chemical shifts in ppm	
1	7.37-7.15	7.37-7.15*	124.5	124.2*
2			125.6	125.2*
3			124.9	124.4*
4			141.6	141.4*
5	4.52	4.61*	72.9	72.7*
6	4.65	4.64*	-	-
7	3.96	4.60*	55.3	54.2*
8	1.01	0.95*	12.5	11.0*
9	2.85	2.80*	24.3	34.6*
10	-	-	171.0	170.0*
11	2.45 & 2.29	2.22* & 2.21*	23.4	23.6*
12	1.04	1.02*	6.6	6.2*

Table 11: ^{1}H and ^{13}C chemical shifts of pseudoephedrine amide 28. Asterisk denotes one rotamer from another.

The proton NMR of amide **28** indicated a 1:1 mixture of rotamers with the chemical shifts of the protons and carbons indicated in **Table 11**. The coupling constant between the proton on the stereogenic centre C-7 and the other proton on the stereogenic centre C-5 was found to be 8.4 Hz. With this coupling constant in hand this allowed to the determination of the torsion angle between these two protons by using Sweet *J*.[36]

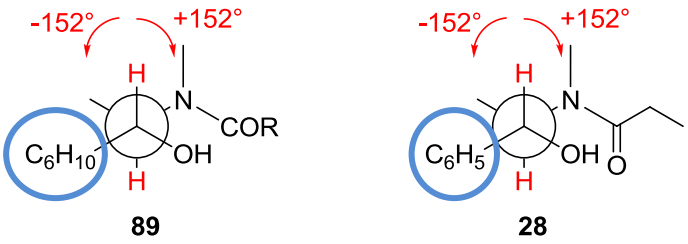


Figure 12: Sweet *J* torsion angle determination.

The closest similar structure to amide **28** was the amide **89** for the computer program. By applying the coupling constant of 8.4 Hz to **89** the computer program predicted a torsional angle between the C-1 and C-2 protons of -152° or +152° (**Figure 12**)[36] indicating that they are not entirely *trans* coplanar. Structure **89** is similar to amide **28** differing only by a different ring system in blue (RCON= amide with R=alkyl) indicating that this torsion angle can be related to C-5 and C-7 protons of amide **28**. This strongly indicates that the amide **28** probably exists in solution as extended conformers. Furthermore, the nOe signals detected (**Appendix 3**) provided evidence for the conformation of the two amide rotamers of **28** (**28**$^{\#}$ **Figure 13** and **28**$^{\#\#}$ **Figure 14**).

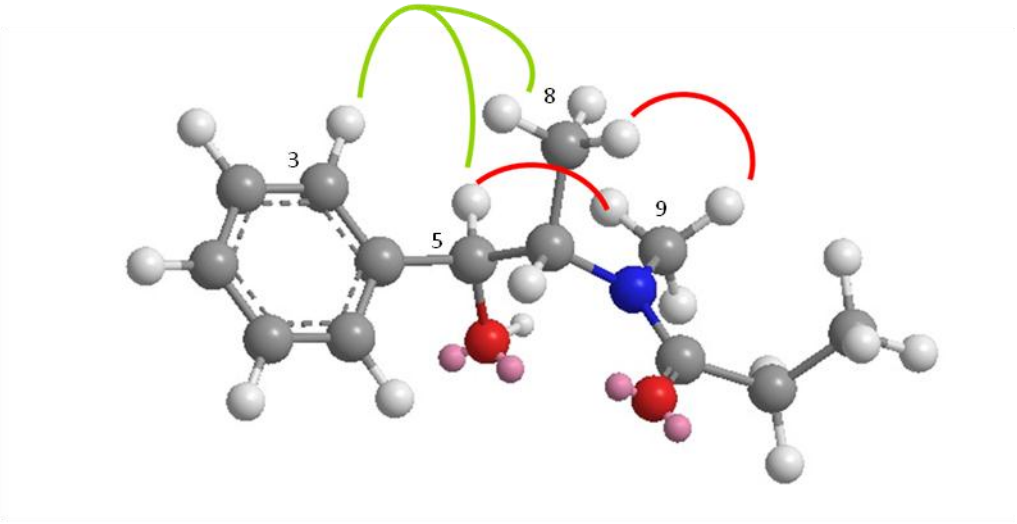


Figure 13: Amide rotamer 28$^{\#}$ with an *anti* conformation for the *N*-methyl and C-7 methine.

Cross peaks between the aryl *ortho* proton C-3 and the C-5 proton as well as the C-8 methyl supported the structure of **28**$^{\#}$ (**Figure 13**). Moreover, the nOe signal between the *N*-methyl and the C-5 proton as well as with the C-8 methyl also

indicates the suggested structure **28**$^{\#}$ (**Figure 13**). These signals suggest an extended conformation for amide **28** with an *anti* arrangement for the *N*-methyl and C-7 methine.

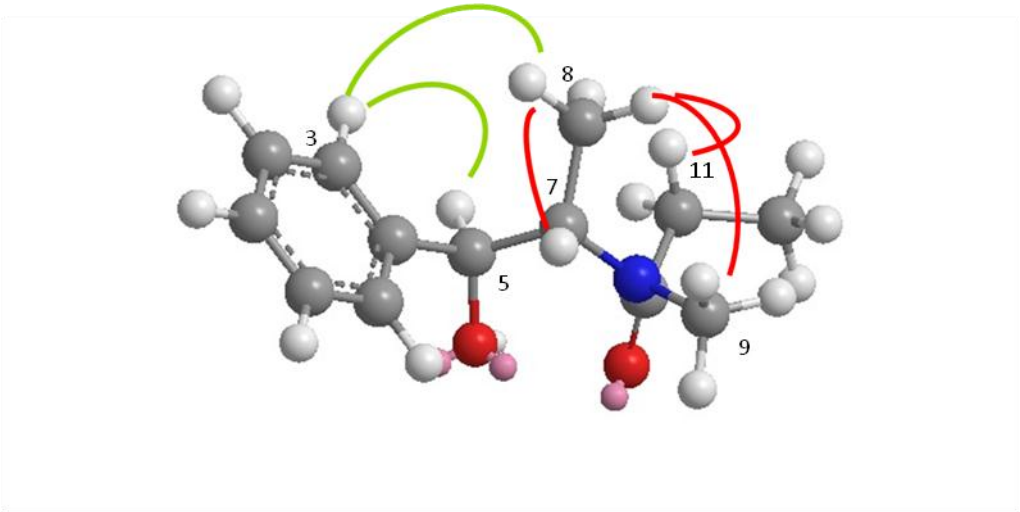
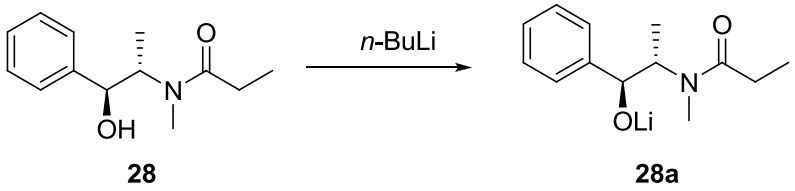


Figure 14: Amide rotamer 28$^{\#\#}$ with a *syn* conformation for the *N*-methyl and C-7 methine.

Concerning the second amide rotamer **28**$^{\#\#}$ (**Figure 14**), cross peaks between the aryl *ortho* C-3 proton and the C-5 methine as well as the C-8 methyl also supported the structure of **28**$^{\#\#}$. Furthermore, nOe signals between the C-8 methyl protons and the *N*-methyl as well as the C-7 methine and the C-11 protons also indicate the suggested structure **28**$^{\#\#}$. These signals indicate an extended conformation with a *syn* conformation for the *N*-methyl and C-7 methine.

In summary, the NMR study revealed that amide **28** exists in solution as two rotamers in a 1:1 mixture. Both of these rotamers have an extended conformation and they differ at the amide position: **28**$^{\#}$ with an *anti* conformation and **28**$^{\#\#}$ with a *syn* conformation for the *N*-methyl and C-7 methine.

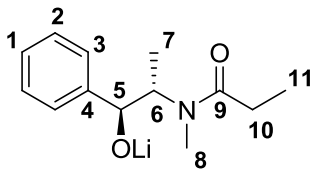
2. Pseudoephedrine alkoxide **28a**



28 **28a**

Scheme 112: Synthesis of pseudoephedrine alkoxide 28a.

In a dry flask under an inert atmosphere, the pseudoephedrine amide **28** (**Scheme 42**), in THF, was deprotonated by 1 equivalent of *n*-BuLi at -78 °C. The alkoxide **28a** was isolated by evaporation of the solvent and was added to a purged NMR tube. The resulting alkoxide **28a** was subjected to NMR investigations in tetrahydrofuran-d_8 including ^{1}H, ^{13}C, HSQC and NOESY (**Appendix 4**).



28a

Figure 15: Pseudoephedrine alkoxide 28a.

The proton NMR of the alkoxide **28a** also indicated a 1:1 ratio of rotamers each with a coupling constant of 8.4 Hz between the C-5 and C-6 protons. Again this suggested a torsion angle of -152 ° or 152 ° indicating an extended conformation. The chemical shifts of the protons and carbons of alkoxide **28a** are shown in **Table 12** for both rotamers.

Alkoxide **28a** Carbon No.	^{1}H chemical shifts in ppm		^{13}C chemical shifts in ppm	
1	7.38-7.18	7.38-7.18*	126.36	126.10*
2			127.45	127.09*
3			126.76	126.24*
4			143.45	143.24*
5	4.52	4.64*	74.79	74.52*
6	3.97	4.61*	57.12	55.53*
7	0.95	0.91*	14.31	12.84*
8	2.85	2.80*	25.45	30.02*
9	-	-	172.66	172.12*
10	2.42 & 2.29	2.23* & 2.22*	25.16	26.12*
11	1.04	1.02*	8.44	8.09*

Table 12: ^{1}H and 13C chemical shifts for pseudoephedrine alkoxide 28a. Asterisk denotes one rotamer from another.

Using these NMR data we were able to suggest structures for the two conformations that the alkoxide adopts **28a$^{\#}$** and **28a$^{\#\#}$** (**28a$^{\#}$ Figure 16** and **28a$^{\#\#}$ Figure 17**).

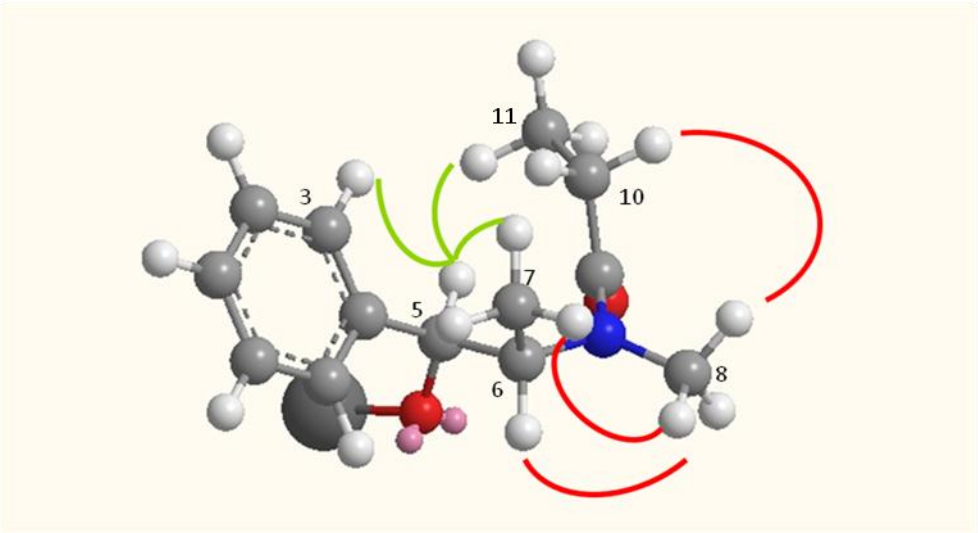


Figure 16: Alkoxide rotamer 28a$^{\#}$ with a *syn* conformation for the *N*-methyl and C-6 methine.

Cross peaks between the C-5 proton and the aryl *ortho* proton C-3 as well as the C-7 methyl and the C-11 methyl supported the structure of **28a$^{\#}$** (**Figure 16**). Furthermore, nOe signals between the *N*-methyl C-8 and the C-7 methyl protons and C-6 proton as well as the C-10 protons also indicate the suggested structure **28a$^{\#}$**. These nOe signals indicate an extended conformation for the alkoxide **28a** where the *N*-methyl and C-6 methine are *syn*.

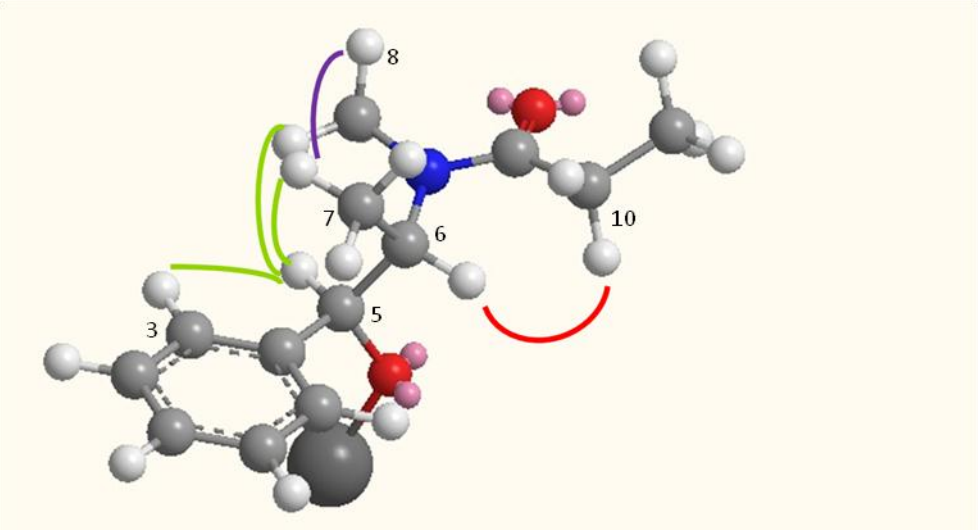


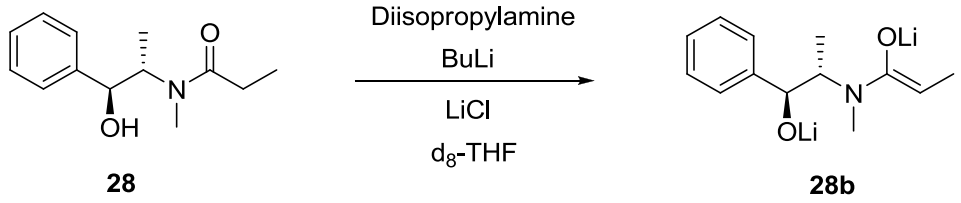
Figure 17: Alkoxide rotamer 28a$^{\#\#}$ with an *anti* conformation for the *N*-methyl and C-6 methine.

As for the other alkoxide rotamer **28a**$^{\#\#}$ (**Figure 17**), nOe signals between the C-5 methine and the aryl *ortho* proton C-3 as well as the C-7 methyl and the *N*-methyl protons C-8 supported the structure of **28a**$^{\#\#}$. Moreover, cross peaks between the *N*-methyl C-8 and the C-7 methyl protons but also cross peaks between the C-6 proton and C-10 protons both indicate the suggested structure **28a**$^{\#\#}$. These cross peaks indicate an extended conformation of the alkoxide **28a** with the *N*-methyl and C-6 methine *anti* to each other.

Therefore, the NMR study of the alkoxide **28a** has given us insight on the conformation adopted. The alkoxide exists in solution as two rotamers that are in an extended conformation. They differ from the amide position: **28a**$^{\#}$ with *N*-methyl and C-6 methine in a *syn* conformation and **28a**$^{\#\#}$ in an *anti* conformation.

3. Pseudoephedrine enolate **28b**

The last important NMR study was of the pseudoephedrine enolate **28b** (**Scheme 43**).

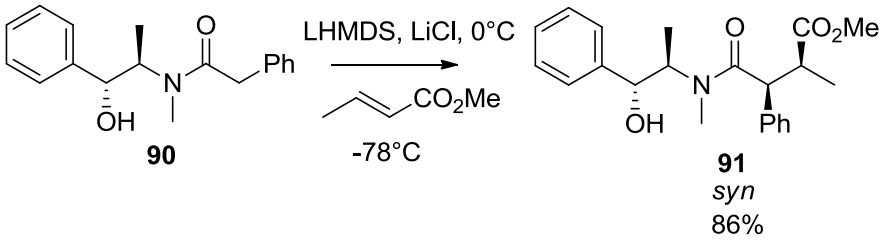


28 **28b**

Scheme 43: Isolation of the enolate 28b.

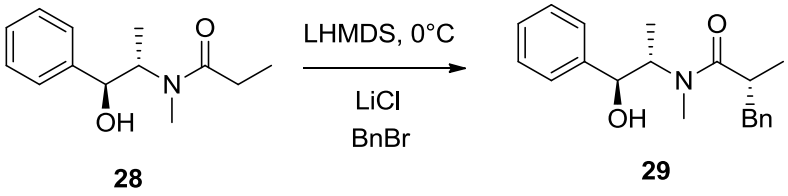
The first attempt at the formation of the enolate **28b** was carried out using LDA in tetrahydrofuran-d_8 at -78 °C whereupon the amide **28** was added. The same time lengths were used as **Table 7** entry **3**. After warming the reaction back up to 0 °C, the enolate **28b** was transferred to a previously purged and sealed NMR tube with a gas tight syringe. Analysis of the isolated material by ^{1}H, ^{13}C, HSQC and NOESY was carried out. Unfortunately the proton NMR showed the presence of the CH_2 present in the amide acyl side chain (C-11 on amide **28**). This suggested that the enolate **28b** had not formed but indicated the presence of the amide **28**. Moreover

the proton NMR was complex because of the presence of hexane (from the *n*-Buli solution in hexane) and also the presence of diisopropylamine. Therefore alternative methods of enolate formation were investigated.



Scheme 44: Michael addition using LHMDS to form the enolate.

In this context, Smitrovich *et al.* used lithium bis(trimethylsilyl)amide (LHMDS) in the presence of LiCl at 0 °C to deprotonate the amide **90** which was then treated with methyl crotonate (**Scheme 44**).[37] This Michael addition gave *syn*-**91** in good yield. This deprotonation protocol was deemed to be attractive for our NMR studies in the formation of the enolate **28b** from amide **28**.



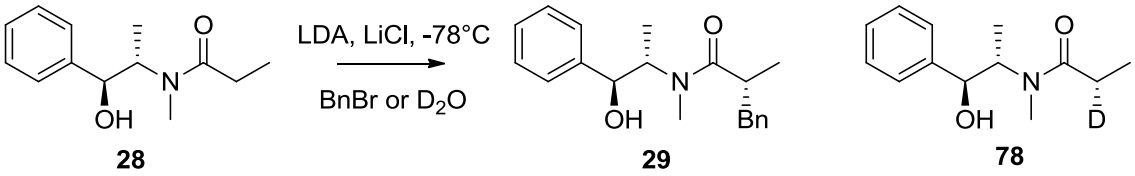
Scheme 45: Alkylation using LHMDS for deprotonation.

Before directly trying this new protocol for the NMR study we decided we should try and alkylate the enolate derived from the amide **28** with benzylbromide (**Scheme 45**).

	LHMDS 2 eq.	Temperature addition LHMDS	Yield **29**
1	Commercial solid	rt	-
2	Solution made with commercial solid @ 0.9 M	rt	-
3	In house solution with in house LHMDS @ 0.86 M	rt	-
4	In house solution with in house LHMDS @ 0.49 M	0 °C	-

Table 13: Conditions used for the formation of 29.

The first attempt at the enolate **28b** formation involved adding commercial solid of LHMDS to a solution of the amide **28** in anhydrous THF at 0 °C. In this case, no product **29** was isolated only starting material **28** (**Table 13 entry 1**). We decided then to use the same conditions that Smitrovich *et al.* used to form the enolate of **90'** by utilizing a solution of LHMDS.[37] A solution using commercially available LHMDS in THF (0.9 M) was prepared and used to deprotonate amide **28**. Unfortunately only the starting material **28** was recovered (**Table 13 entry 2**). At this point we decided to make LHMDS by treating hexamethyldisilazane with 1 equivalent of *n*-BuLi at -50 °C. This prepared LHMDS was used for the next attempt but resulted in the recovery again of the amide **28** (**Table 13 entry 3**). In this experiment it was observed that the LHMDS did not fully dissolve compromising the concentration and therefore the number of equivalents added. Therefore, a solution of this prepared LHMDS in THF was generated at 0 °C (**Table 13 entry 4**). This solution was added to the amide **28**. However, no product was again produced after treatment with benzylbromide. This can be explained by the fact that the CH_2 of amide **28** is less acidic than the one of amide **90** resulting in no formation of enolate **28b**. These disappointing results forced a re-evaluation of the deprotonation protocol and it was decided to revert to the used of lithium diisopropylamide as used in Myers alkylation (**Scheme 46**).[17]



28 **29** **78**

Scheme 46: Initial alkylation conditions of Myers with BnBr or D_2O.

	Diisopropylamine purification method	*n*-BuLi concentration	BnBr or D_2O	Yield **29** or **78**
1	distilled	2.35 M	BnBr	-
2	distilled	2.35 M	D_2O	-
3	fractional distillation	2.35 M	D_2O	-
4	new bottle and fractional distillation	2.35 M	D_2O	-

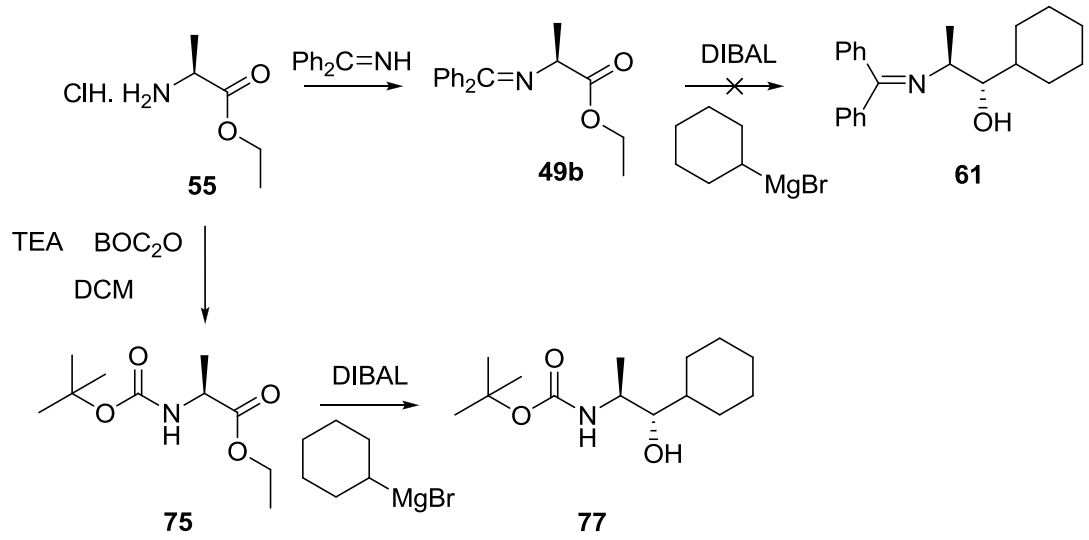
Table 14: Different conditions used for the alkylation of 29 or 78.

With a new bottle of *n*-BuLi freshly titrated at 2.35 M,[29] the alkylation of amide enolate **28a** with BnBr was carried under the same conditions used previously (**Table 7 entry 3**). No product was recovered (**Table 14 entry 1**), so it was decided to investigate whether the enolate formation had been successful by using deuterium oxide as the electrophilic reagent. Using the conditions used previously (**Table 14 entry 1**) for the deprotonation of amide **28** followed by the addition of D_2O did not result in the formation of the deuteriated amide **78** (**Table 14 entry 2**). At this stage it became apparent that the diisopropylamine might have been contaminated with lower boiling impurities. Neither fractional distillation nor the use of fresh sources of this amine proved successful in generating the enolate **28b** (**Table 14 entry 3** and **4**). This suggested that the integrity of the *n*-BuLi was in question. However, time constraints meant that the enolate could not be generated and studied by NMR.

In summary, NMR studies of the amide **28** and the alkoxide **28a** provided an insight into the conformations of the two amide rotamers that these two compounds adopt in solution. We have not yet been able to isolate the enolate and carry out NMR experiments on it.

Conclusions

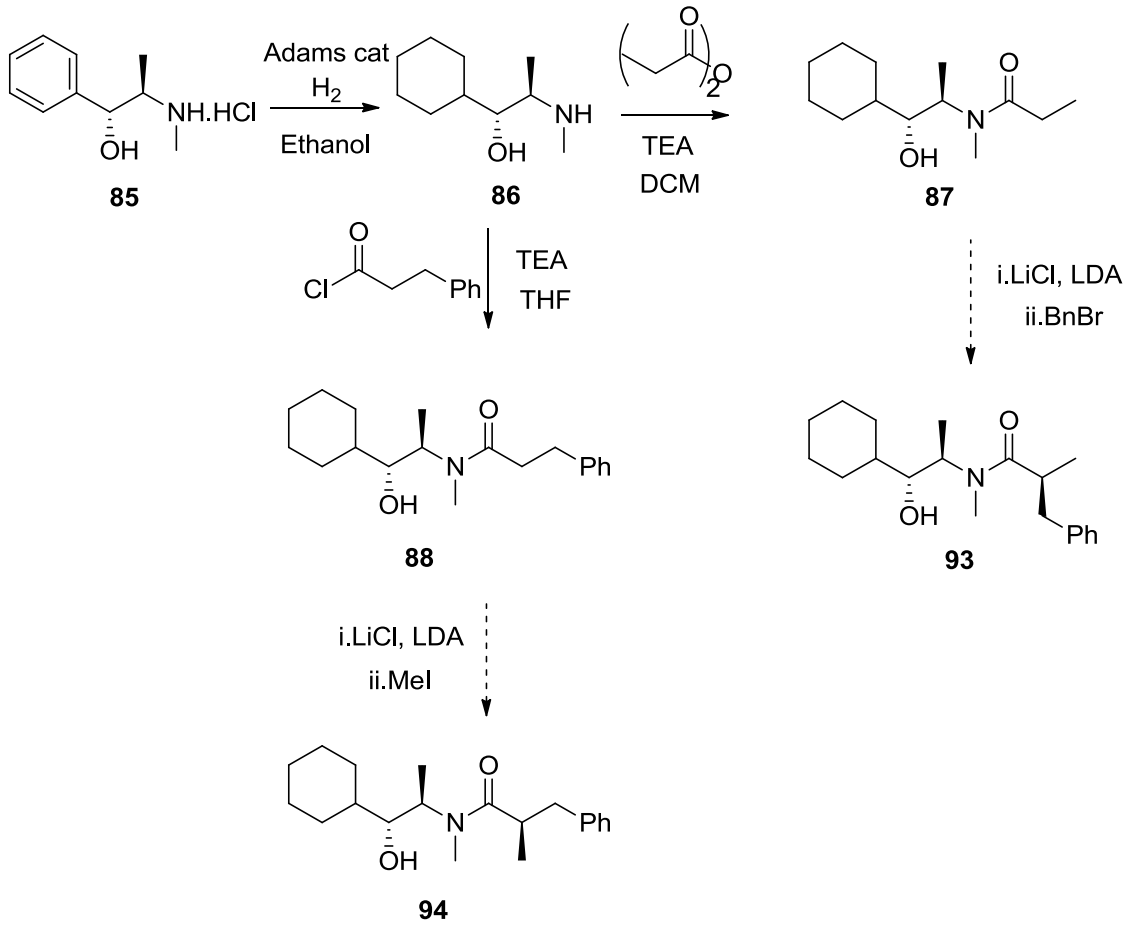
Using Schiff's base protected alanine ester **49b** and Boc protected ester **75** proved to be an ineffective method for the reductive alkylation with the sterically more demanding Grignard reagent cyclohexylmagenium bromide. The latter route provided access to the Boc amino alcohol **77** in a 3:1 mixture of the desired diasteroisomer in 33%. A further purification enabled us to isolate 6% of the major diastereoisomer.



Scheme 47: Synthetic route tried to obtain pseudoephedrine amide analogue 40.

This method was not suitable to prepare compounds using more sterically demanding Grignard reagents. Therefore, a new route was developed for the synthesis of the cyclohexyl pseudoephedrine amide **40** and involved one step by the hydrogenation of (*1R*,*2R*)-pseudoephedrine hydrochloride salt **85** (**Scheme 48**). The cyclohexyl derivative **86** was then *N*-acylated with propionic anhydride which gave the cyclohexyl pseudoephedrine amide **87**. Similarly the cyclohexyl derivative **86** was *N*-acylated with hydrocinnamoyl chloride to obtain the amide **88**. The importance in synthesising both of these amides **87** and **88** was to subject these materials to the diastereoselective alkylation to provide routes to diastereoisomers **93** and **94**. Preparation of these two diastereoisomers **93** and **94** was important to be

able to rapidly identify the diastereoisomer ratios in these alkylation reactions. Due to time constraints the alkylation of these derivatives has not been attempted.



Scheme 48: Route to obtain the pseudoephedrine amide derivatives.

As for the NMR study, we were able to suggest solution phase structures for the amide **28** and alkoxide **28a** of the two rotamers present in solution for each (**28**$^{\#}$ and **28**$^{\#\#}$ represented in **Figure 13** and **Figure 14** and **28a**$^{\#}$ and **28a**$^{\#\#}$ for the latter in **Figure 16** and **Figure 17**).

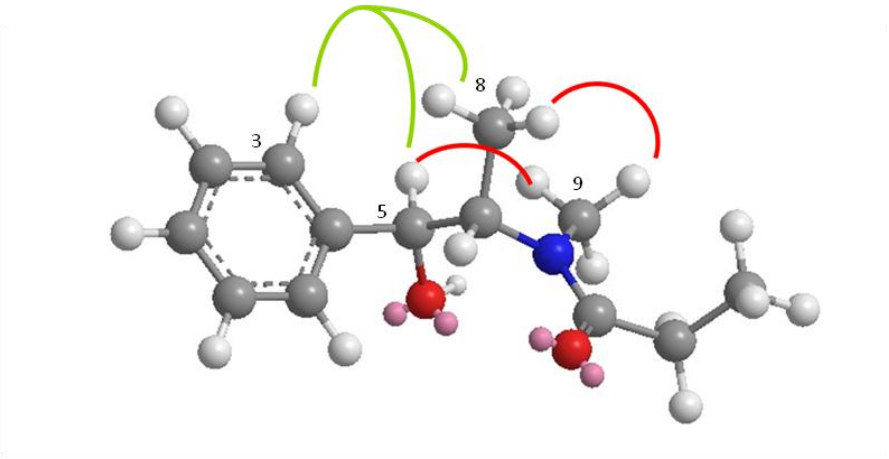


Figure 13: **Amide rotamer 28[#] with a *trans* conformation for the *N*-methyl and C-7 methine.**

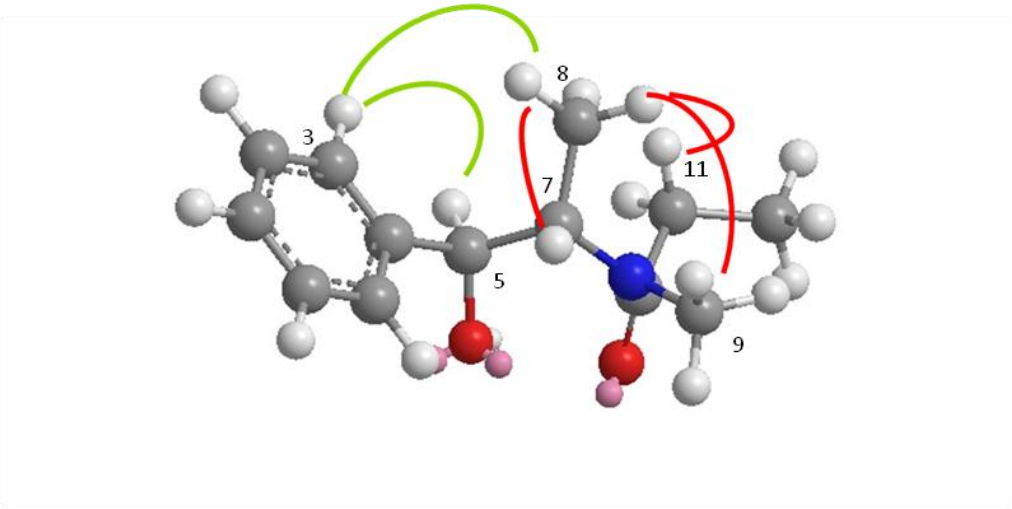


Figure 14: **Amide rotamer 28[##] with an *anti* conformation for the *N*-methyl and C-7 methine.**

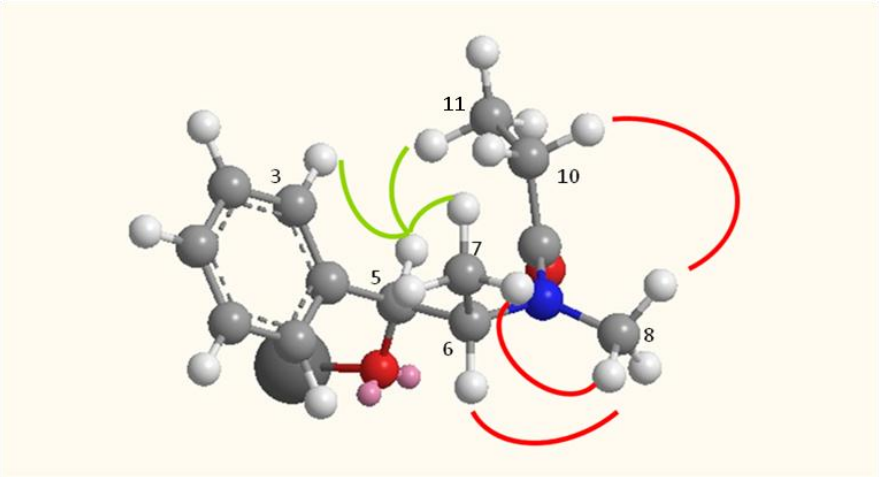


Figure 16: **Alkoxide rotamer 28a[#] with a *syn* conformation for the *N*-methyl and C-6 methine.**

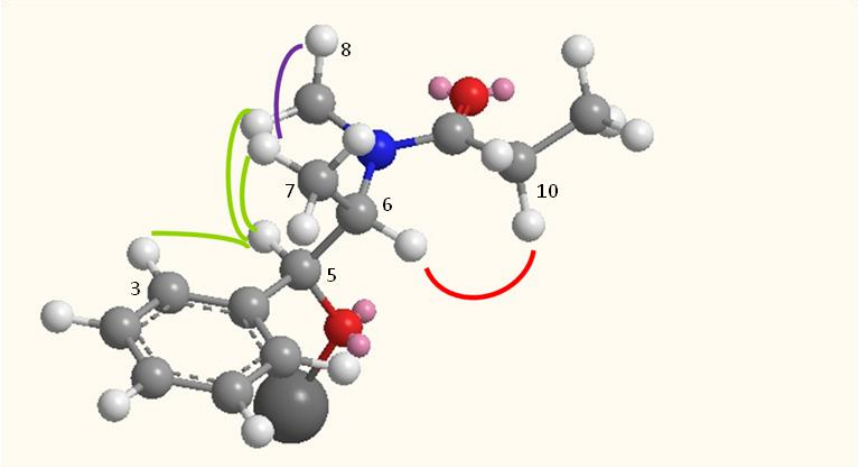
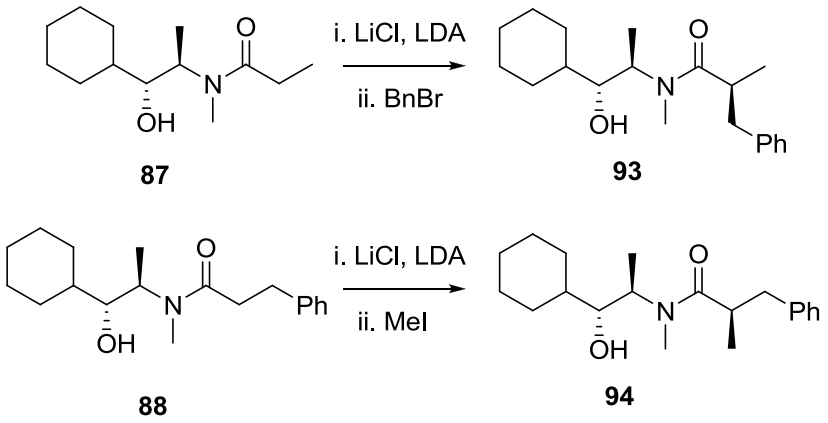


Figure 17: **Alkoxide rotamer 28a[##] with an *anti* conformation for the *N*-methyl and C-6 methine.**

The results suggest an extended conformation in both cases for both rotamers with only the geometry about the amide that differs. Unfortunately it has not been possible to isolate the enolate and carry out the NMR experiments.

Future work

In the future, the new cyclohexyl pseudoephedrine amides **87** and **88** need to undergo alkylation. The alkylation of amide **88** with MeI while benzylating amide **87** will provide the diastereomeric derivatives **94** and **93** respectively. **Scheme 49**.

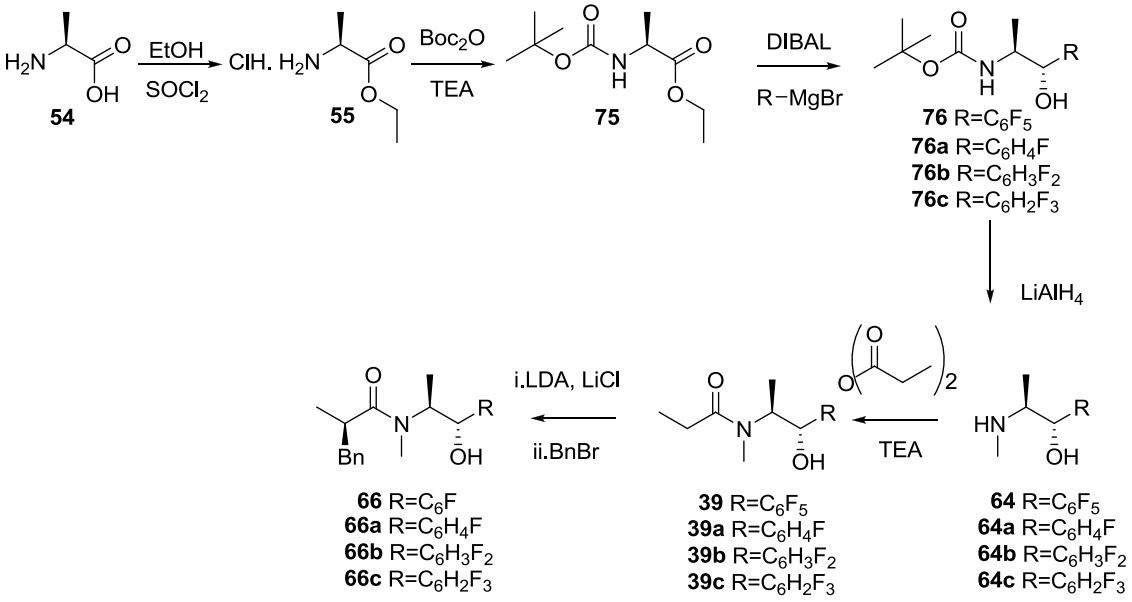


87 **93** **88** **94**

Scheme 49: Alkylation of amides 87 and 89 to afford the two diastereoisomer 93 and 94.

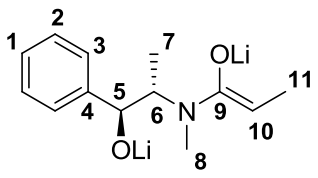
Myers' method will be applied in order to do a diastereomeric ratio analysis by chiral HPLC[17] or by cyclisation.[38] With these results we will be able to know if by changing the electron density of the ring we changed the diastereoselective outcome of the reaction. It must be noted that if we do not see a lower diastereoselectivity this would imply that our hypothesis is no longer valid. The pentafluorophenyl pseudoephedrine amide derivative **39** also needs to be synthesized in order to have another example of electron poor rings. As stipulated earlier, we were planning on synthesising this derivative by using the pentafluorophenyl magnesium bromide as the Grignard reagent (see **Scheme 50**). The pentafluoro Grignard is no more sterically demanding than phenylmagnesium halides as fluorine is about the same size as hydrogen. What might be problematic in this Grignard approach is the fact that fluorine is more electron rich than hydrogen. This route needs to be verified. Furthermore, other derivatives with one, two or three fluorines on the aromatic ring of the Grignard will also be tested to synthesize amino alcohol **76a**, **76b** or **76c**. They might be easier to synthesize as the Grignard will have less electron rich atoms

on the aromatic ring. They would still provide us some insight as the fluorine element has a very strong electronegativity which would still imply a less important π-Li interaction during the alkylation.



Scheme 50: Route to synthesize fluorinated aromatic ring pseudoephedrine derivatives.

Moreover the enolate NMR study of pseudoephedrine **28b** (**Figure 18**) must be carried out and continued. It would maybe be interesting to use commercially available LDA and titrate it in order to determine its concentration before using it. This might lead us to isolate the enolate **28b** and therefore analyse it by ^{1}H, ^{13}C and NOESY experiments. With the *J* value of C-5 and C-6 protons as well as the nOe signals and ^{13}C chemical shifts we would be able to determine the configuration the enolate **28b** adopts during this alkylation process.



28b

Figure 18: Enolate 28b.

Experimental

^{1}H, ^{13}C, NOESY NMR were carried out on a Bruker DPX-400 (or other NMR instruments such as DPX-500 and DPX-600) spectrometer with chemical shifts given in ppm (δ values), relative to the residual proton resonances in deuterated solvents for ^{1}H NMR and also relative to solvent in ^{13}C NMR. The ^{1}H NMR signals are reported by: m (multiplet), d (doublet), s (singlet), t (triplet), br (broad) and constant values *J* are recorded in Hz.

IR spectra were recorded on a Perkin Elmer 1 FT-IR spectrometer with KBr discs made for solids or neat for oils on NaCl plates.

Elemental analysis were carried out on a Perkin Elmer 2400, analyser series 2 in house at the University of Strathclyde.

Accurate mass spectrometry was carried out on a Jeol JMS AX505 using fast atom bombardment or electrospray ionisation.

Melting points were recorded on a Reichert hot stage microscope, and are uncorrected.

Chromatography was carried out using 200-400 mesh silica gels following standard procedure.[39]

Specific rotations were recorded using a Perkin Elmer 341 polarimeter using the sodium D line with a 1 cm^3 10 dm cell at 20 °C with a wavelength of 589nm. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and the concentrations are given in g/100 cm^3.

Thin layer chromatography (TLC) was carried out using pre-coated silica plates (Alugram® Sil G/UV_{254}). Visualisation of TLC plates were achieved by UV (254 nm), or by using a vanillin solution for the detection of amines or a phosphomolybdic acid solution for the detection of alcohols. The vanillin solution was made by adding 250 ml of ethanol to 15 g of vanillin and 2.5 ml of concentrated sulfuric acid. The stains would appear on the TLC plate after heating up the plate dripped in the solution. The phosphomolybdic acid solution was prepared by adding

100 ml of ethanol to 20 g of phosphomolybdic acid. The plate would be heated up after dripping it in this solution in order to reveal the stains.

Dry solvents such as DCM, THF and Et_2O were provided by standard operating procedure for Innovative Technology Solvent Purification System.

Some reagents were distilled prior to use:

Reagent	Dry agent	distillation at normal pressure	distillation at reduced pressure
Diisopropylamine	CaH_2 used during distillation	at 83 °C	
Benzyl bromide	CaH_2 used during distillation		60 °C at 10 mbar
Propionic anhydride	Potassium carbonate mixed then filtered before distillation		50 °C at 10 mbar

Table 15: Distillation conditions.

Different drying methods were used for the pseudoephedrine amide 28 (see **Table 16**). Lithium chloride was left to dry overnight in the chemical oven at 150 °C and then flame dried in the flask under vacuum and finally under nitrogen prior to use.

	Drying method for pseudoephedrine amide 28
1	Drying pistol at 2 mbar overnight
2	Drying pistol at 2 mbar overnight at 40 °C
3	$CaCO_3$ and azeotropic removal of water with toluene
4	$CaCO_3$ and azeotropic removal of water with toluene and then drying pistol at 2 mbar overnight
5	$CaCO_3$ and azeotropic removal of water with toluene and then drying pistol at 2 mbar overnight at 40 °C

Table 16: Different drying methods for pseudoephedrine amide 28.

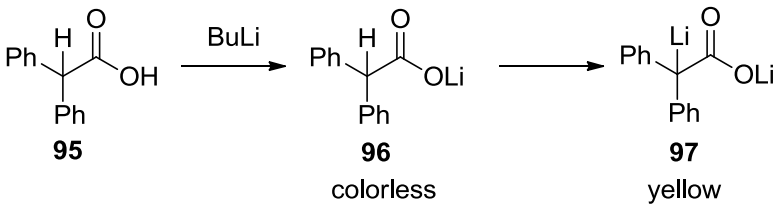
All three-necked flasks were previously dried at 140 °C, flame dried under reduced pressure (2 mbar) and flame dried under inert atmosphere.

All syringes and needles were previously dried at 140 °C and left to cool down in a dry box. They were then put under inert atmosphere.[40]

All compounds were concentrated *via* rotary evaporator at 2 mbar.

The HCl saturated ethanol was prepared by dropping sulfuric acid (10 mL) with a dropping funnel into a stirred solution of concentrated HCl (10 mL). The HCl produced was dried by passage through calcium chloride. The HCl gas was then bubbled through anhydrous ethanol in a sealed flask with a bubbler. The reaction was exothermic so addition was carried out by slow bubbling of HCl through ethanol and an ice bath was occasionally necessary.

Titration of *n*-BuLi:[29]

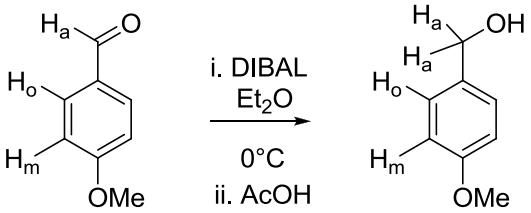


95 **96** colorless **97** yellow

Scheme 51: Titration of *n*-BuLi with diphenyl acetic acid.

Diphenylacetic acid (500 mg, 2.36 mmol) was added to a three-necked flask as well as anhydrous THF (10 mL). *n*-BuLi was then added drop-wise via a 1 mL glass syringe (0.1 mL precision) until the solution reaches the yellow end point. The yellow colour indicates the formation of lithium lithiodiphenylacecate **97** where all the carboxyl protons have been consumed.[29] With the known volume of *n*-BuLi to reach the end point it was possible to deduce the concentration of the solution that was titrated (mmol of X/mL of *n*-BuLi). Two to three attempts were carried out which provided a precise concentration.

Titration of DIBAL:[32]



98 **99**

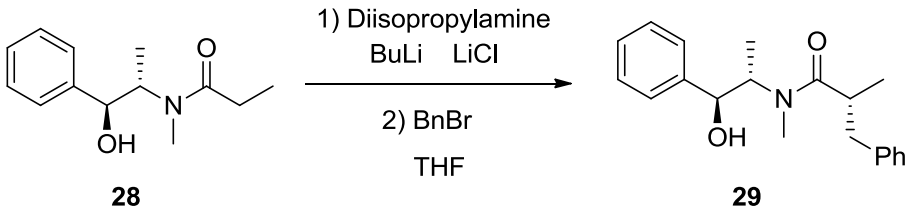
Scheme 52: Ttiration of DIBAL with *p*-anisaldehyde

In a dry three-necked flask under an inert atmosphere, *p*-anisaldehyde (0.27 mL, 2.2 mmol) was added as well as anhydrous Et_2O (3 mL). The solution was left to stir at 0 °C whereupon DIBAL in hexane at 1 M (1.1 mL, 1.1 mmol, 0.5 eq.) was added and left to stir for 5 minutes. Glacial acetic acid was added rapidly to the vigorously stirred solution. An aliquot of the resulting solution was transferred to a NMR tube and a no-D NMR[34] was carried out. A no-D NMR consists of recording a normal ^1H NMR in a non-deuteriated solvent and recording it in unlocked mode.[41] To determine the concentration of DIBAL:

$$[\text{DIBAL-H}] = \frac{(\text{mmol } p\text{-anisaldehyde}) \times (\%\text{conv})}{V_{\text{solution DIBAL-H}}} \quad \text{with} \quad \%\text{conv} = \frac{\text{integral product}}{\text{integral SM + integral product}}$$

This analysis gave a concentration of 0.66 M by using the integration of H_a for the starting material and the product. (A**ppendix 1**)

Preparation of [1*S*,2*S*]-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethylbenzenepropionamide 29:



28 **29**

Scheme 53: Synthesis of 29.

Lithium chloride was left to dry overnight in the chemical oven at 140 °C and the starting material (1*S*,2*S*)-*N*-(2-hydroxy-1-methyl-2phenylethyl)-*N*-methylpropionamide **28** (0.14 g, 0.633 mmol, 1 eq.) was dried overnight under reduced pressure (2 mbar) in a drying pistol. In a dry three-necked flask, lithium chloride (0.16 g, 3.798 mmol, 6 eq.) was charged and the flask was flame dried under reduced pressure (2 mbar). It was left to cool under an inert atmosphere and flame dried again. Anhydrous THF (3 mL) was added as well as freshly distilled diisopropylamine (0.2 mL, 1.424 mmol, 2.25 eq.). The reaction mixture was cooled to -78 °C before the addition of *n*-buthylithium (0.7 mL, 1.329 mmol, 2.1 eq.) that was previously titrated at 1.88 M.[29] The solution was then briefly warmed to 0 °C for 15 minutes and then cooled to -78 °C. An ice cooled solution of the dried amide **28** (0.14 g, 0.633 mmol, 1 eq.) in anhydrous THF (3 ml) was added to the reaction. The solution was left to stir for 1 hour at -78 °C, than 1 hour at 0 °C and finally 40 minutes at room temperature before bringing it back to 0 °C. Freshly distilled benzyl bromide (0.112 mL, 0.9495 mmol, 1.5 eq.) was then added and left to stir for 40 minutes at 0 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl (5 mL) and the product was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography (20% ethyl acetate/ 80% hexane) to give a colourless oil **29** with a yield of 71% (140 mg, 0.45 mmol). A portion (53 mg) of product was recrystallized from hot toluene to afford 24 mg of a white powder.

^{1}H NMR: (4.3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 400 MHz in CDCl3) **δ** 7.4-7.15 (m, 10H), 4.55 (m, 1H), 4.44 (br, 1H), 4.08*(br, 1H), 4.02* (m, 1H), 3.15* (m, 1H), 2.94 (m, 2H), 2.93 (m, 1H), 2.87* (s, 3H), 2.68 (s, 3H), 2.65* (m, 2H), 1.16 (d, 3H, *J*=4.8 Hz), 1.12* (d,3H, *J*=5.2 Hz), 0.98* (d, 3H, *J*=5.6 Hz), 0.96 (d,3H, *J*=5.6 Hz)

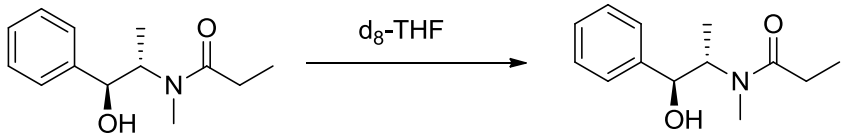
^{13}C NMR: (125 MHz in $CDCl_3$) **δ** 178.39 (C=O), 142.37 (quaternary phenyl C), 140.00 (quaternary phenyl C), 129.20, 128.99, 128.72, 128.43, 128.40, 128.34, 127.65, 126.90, 126.45, 126.26, 76.60, 40.40, 38.98, 33.20, 17.51, 14.35

IR Spectroscopy (KBr, cm^{-1}): 3313 (br, OH), 1614 (C=O), 697 (5-adj aromatic C-H)

HRMS: found M+H=312.1952 calculated for $C_{20}H_{26}O_2N$ M+H=312.1958

Melting point: 117-119 °C (lit. 136-137 °C)[17]

NMR study of *N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylpropanamide 28:



Scheme 54: NMR study of 28

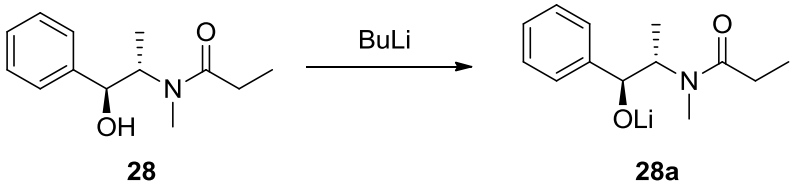
N-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylpropanamide **28** (12 mg) was left to dry overnight in a drying pistol under reduced pressure (2 mbar). To an NMR tube purged with nitrogen was added the dried amide. THF-d_8 was added through neutral alumina to remove traces of water.

^{1}H NMR: (1:1 rotamer ratio, asterisk denotes one from the other, 400 MHz in d_8-THF) **δ** 7.37-7.15 (m, 10H includes both rotamers), 4.65 (d, 1H, *J*=2.8 Hz), 4.64 (br, 1H)*, 4.61 (br,1H)*, 4.6 (br, 1H)*, 4.52 (dd, 1H, *J*= 8.4, 2.8 Hz), 3.96 (m, 1H), 2.85

(s, 3H), 2.8 (s, 3H)*, 2.45 (m, 1H), 2.29 (m, 1H), 2.22 (q, 1H, *J*=7.6 Hz)*, 2.21 (q, 1H, *J*=7.6 Hz)*, 1.04 (t, 3H, *J*=7.6 Hz), 1.02 (d, 3H, *J*=6.8 Hz)*, 1.01 (t, 3H, *J*=7.6 Hz)*, 0.95 (d, 3H, *J*=6.8 Hz)

^{13}C NMR: (1:1 rotamer ratio, asterisk denotes one from the other, 100 MHz in d_8-THF) **δ** 171.00, 170.00* (C=O), 141.60, 141.40*, 125.60, 125.20*, 124.90, 124.50, 124.40*, 124.20*, 72.90, 72.70*, 55.30, 54.20*, 34.60*, 24.30, 23.60*, 23.40, 12.50, 11.00*, 6.60, 6.20*

NMR studies and preparation of the alkoxide 28a:



28 **28a**

Scheme 42: Synthesis and NMR study of alkoxide 28a

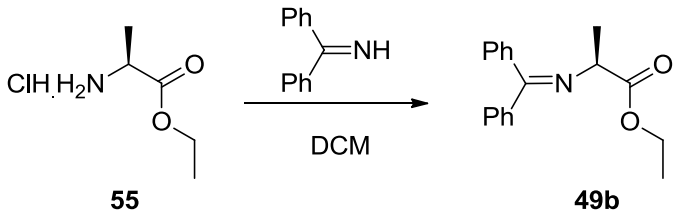
In a dry three-necked flask, was added the *N*-[(*S*,*S*)-*N*-(2-hydroxy-1-methyl-2phenylethyl)]-*N*-methylpropionamide **28** (0.06 g, 0.27 mmol, 1 eq.) and anhydrous THF (1 ml). The solution was left to stir under inert atmosphere at -78 °C, before the addition of *n*-BuLi (0.14 mL, 0.27 mmol, 1 eq.) previously titrated at 1.88 M.[29] The solution was brought back up to room temperature before the THF was evaporated (2 mbar). A nitrogen purged NMR tube was charged with a solution of alkoxide formed **28a** (4 mg, 0.018 mmol) in dry d_8-THF (1 mL through neutral alumina).

^{1}H NMR: (1:1 rotamer ratio, asterisk denotes one from the other, 400 MHz in $CDCl_3$) **δ** 7.38-7.7.18 (m, 10H), 4.64 (broad, 1H)*, 4.61 (broad, 1H)*, 4.52 (d, 1H, *J*=8.4Hz), 3.97 (m, 1H), 2.85 (s, 3H), 2.80 (s, 3H)*, 2.42 (m, 1H), 2.29 (m, 1H), 2.23 (q, 1H, *J*=7.6 Hz)*, 2.22 (q, 1H, *J*=7.6 Hz)*, 1.04 (t, 3H, *J*=7.6 Hz), 1.02 (t, 3H, *J*=7.6 Hz)*, 0.95 (d, 3H, *J*=6.8 Hz), 0.91 (d, 3H, *J*=6.8 Hz)*

^{13}C NMR: (1:1 rotamer ratio, asterisk denotes one from the other, 100 MHz in $CDCl_3$) **δ** 172.66 (C=O), 172.12 (C=O)*, 143.45 (quaternary phenyl C), 143.24*,

127.45, 127.09*, 126.76, 126.36, 126.24*, 126.10*, 74.79, 74.52*, 57.12, 55.53*, 30.20*, 26.12*, 25.45, 25.16, 14.31, 12.84*, 8.44, 8.09*

Preparation of Ethyl (2*S*)-2-[(diphenylmethylene)amino]propanoate 49b:



55 **49b**

Scheme 28: Synthesis of 49b.

The starting material ethyl (2*S*)-2-aminopropanoate hydrochloride **55** (previously synthesized by Coti[25]) was dried overnight under reduced pressure (2 mbar). In a 3 necked flask previously dried in the oven (140 °C), was added a solution of the hydrochloride salt **55** (4 g, 26.07 mmol, 1 eq.) in dry DCM (30 mL) under inert atmosphere. Benzophenone imine (95% pure, 4.6 ml, 26.07 mmol, 1 eq.) was added to the solution. The reaction was left to stir for 3 days. The resulting ammonium chloride was filtered and the filtrate concentrated at reduced pressure (2 mbar). The residue was then dissolved in ether (30 mL), filtered and washed with H_2O (3 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to afford a yellow oil. The resulting oil was triturated in cold hexane to give light yellow crystals 5.86 g (80% yield).

^{1}H NMR: (400 MHz in $CDCl_3$) **δ** 7.85-7.2 (m, 10H), 4.19 (m, 3H CH_2 and CH), 1.45 (d, 3H, *J*=6.8 Hz), 1.28 (t, 3H, *J*=7.2 Hz)

^{13}C NMR: (100 MHz in $CDCl_3$) **δ** 172.40 (C=O), 169.20 (C=N), 139.00, 135.80 (quaternary aromatic), 129.80, 129.60, 128.29, 128.13, 128.08, 127.79, 127.56, 127.21 (aromatic), 60.40 (CH_2), 60.20 (CH), 18.70, 13.70

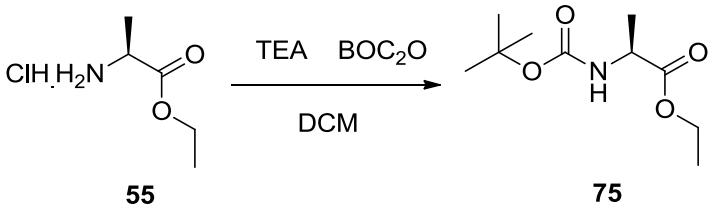
IR Spectroscopy (KBr, cm^{-1}): 1735, 1625, 1449, 1376, 1285, 1197, 1127, 779, 704

HRMS: found M+H=282.1484 calculated for $C_{18}H_{20}O_2N$ M+H= 282.1489

Melting point: 50-52 °C (lit. melting point= 52-53 °C)[24]

$[\alpha]_D$=-81.3 (c=2, $CHCl_3$) (lit. $[\alpha]_D$= -90 (c=2, $CHCl_3$))[24]

Preparation of Ethyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]propanoate 75:



55 **75**

Scheme 34: Synthesis of 75.

The ethyl (2*S*)-2-aminopropanoate hydrochloride **55** (previously synthesized by Coti[25]) (4.18 g, 27.21 mmol) was dried in the drying pistol (2 mbar) overnight. In a dry 3 necked flask, was added a solution of the salt **55** in anhydrous DCM (50 ml) under an inert atmosphere. Dry triethylamine (7.6 mL, 54.42 mmol) was added slowly to the solution to form the free base. The solution was left to stir for 30 minutes before the addition of di-*tert*-butyl dicarbonate. The reaction was left to stir for 5 days. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (30 mL). The product was extracted with DCM (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated (2 mbar). The crude was purified by flash chromatography (20% ethyl acetate/80% hexane) to recover a yellowish oil. (5.38 g, 91%)

^{1}H NMR: (400 MHz in $CDCl_3$) **δ** 5.08 (broad, 1H from NH), 4.30 (m, 1H), 4.20 (q, 2H, *J*= 7.2 Hz), 1.46 (s, 9H), 1.39 (d, 3H, *J*=7.2 Hz), 1.29 (t, 3H, *J*= 7.2 Hz)

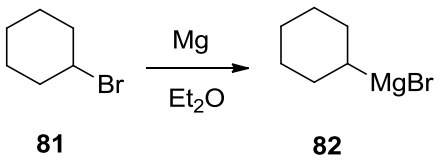
^{13}C NMR: (100 MHz in $CDCl_3$) **δ** 172.90 (C=O), 154.62 (C=O of BOC), 79.27, 60.79, 48.74, 27.90, 27.82, 27.67, 18.21, 13.64

IR spectroscopy (Liq., cm^{-1})**:** 3366 (br. s, NH), 2981, 2937, 1718 (br., 2 × C=O), 1517, 1455

HRMS: M+H=218.1389 calculated for $C_{10}H_{20}O_4N$ M+H=218.1390

$[\alpha]_D$= -41.8 (c=1, MeOH) (lit. $[\alpha]_D$ = -42.5 (c=1, MeOH))[42]

Preparation of cyclohexylmagnesium bromide 82:



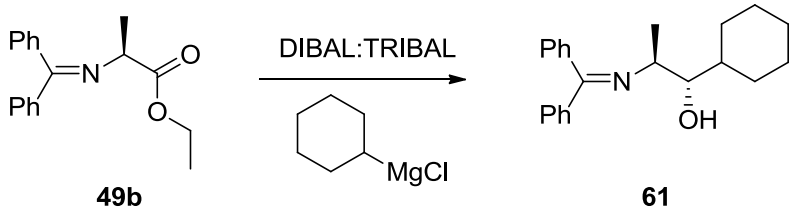
Scheme 35: Synthesis of Grignard 82.

In a dry three-necked flask previously dried in the oven 140 °C, was added magnesium turnings (15.8 g, 0.65 mmol, 6.5 eq.). The flask was then put under reduced pressure (2 mbar), flame dried then put under nitrogen and flame dried again. The turnings were left to stir vigorously overnight in order to activate them.[33] The next day, diethyl ether (8 mL) was added in order to cover the turnings and a dry condenser was added as well. The solution was stirred vigorously; the freshly distilled cyclohexyl bromide (12.3 mL, 0.1 mmol) was added very slowly *via* syringe pump into the vortex of the solution.[33] The addition was done slowly as to always maintain a slight reflux. Excessive reflux was controlled by cooling the mixture by way of an external ice bath. The solution was stirred for 2 h under reflux and then was transferred to a dry sealed flask.

The titration of the Grignard formed was based on a no-D method (no-deuterium proton NMR).[34] This used cyclooctadiene as the reference (100 μL) in a tared NMR tube under nitrogen where the Grignard (600 μL) was then added. The no-D proton NMR was recorded and used to deduce the concentration of the Grignard and found to be 0.41 M. (**Appendix 2**)

Preparation of (1*S*,2*S*)-1-cyclohexyl-2-[(diphenylmethylene)amino]-1-propanol 61:

- **Adaptation of Polt's[24] phenylmagnesium bromide conditions:**



49b **61**

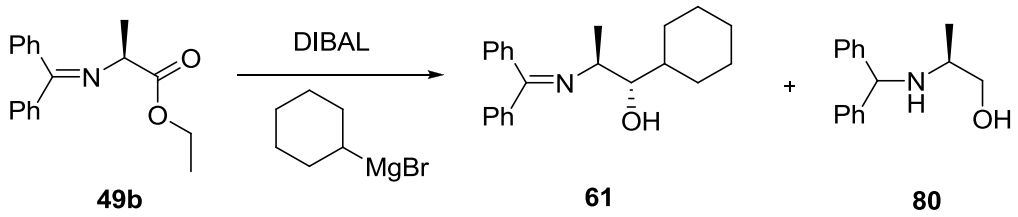
Scheme 55: **Synthesis of 61.**

The starting material ethyl (2*S*)-2-[(diphenylmethylene)amino]propanoate **49b** (0.348 g, 1.237 mmol, 1 eq.) was left to dry overnight in the drying pistol under reduced pressure (2 mbar). Anhydrous DCM (20 mL) was added to the dried starting material **49b** under inert atmosphere and transferred to the dry three-necked reaction flask by cannula. The reaction was left to stir and cool to -78 °C. In a separate dry three-necked flask, a 1:1 solution of DIBAL:TRIBAL was prepared under an inert atmosphere by adding DIBAL (0.66 M,[32] 1.87 ml, 1.237 mmol, 1 eq.) and TRIBAL (1 M, 1.24 mL, 1.237 mmol, 1 eq.). The 1:1 solution was added slowly *via* syringe pump to the solution of the ester **49b** at -78 °C. The solution was left to stir for 5 hours at -78 °C before the drop-wise addition of cyclohexylmagnesium chloride (2 M, 1.86 mL, 3.711 mmol, 3 eq.) at. Once the addition was complete, the reaction was left to warm to room temperature for 20 hours. The solution was quenched slowly by drop-wise addition of a saturated solution of $NaHCO_3$ (10 mL) at 0 °C. The product was extracted with DCM (3 × 30 mL), the combined organic layers dried over Na_2SO_4, filtered and concentrated into a yellow oil. The resulting oil was purified by flash chromatography (5-20% ethyl acetate/85-50% hexane). Another flash chromatography was necessary (2.5% DCM/ 2.5% EtOAc/ 95% hexane) where 73 mg (18%) of assumed product **61** was isolated.

^{1}H NMR: (400 MHz in $CDCl_3$) **δ** 7.80-7.20 (m, 10H), 3.58 (td, 1H, J_1= 9.2 Hz, J_2= 8.0 Hz), 2.09 (m, 1H), 1.90 (m, 1H), 1.40-1.02 (m, 10H), 1.22 (d, 3H, J=6.4Hz)

^{13}C NMR: (100 MHz in $CDCl_3$) **δ** 145.20 (C=N), 131.90 (quaternary C), 129.00 (quaternary C), 127.60 (2C), 127.30 (2C), 126.80, 126.50, 125.70 (2C), 125.00 (2C), 83.00, 59.00, 44.00, 25.60, 23.90, 22.90, 22.10, 21.90, 16.00

- **Adaptation of Zhao's[27] allylmagnesium bromide conditions:**



49b **61** **80**

Scheme 32: Synthesis of 61.

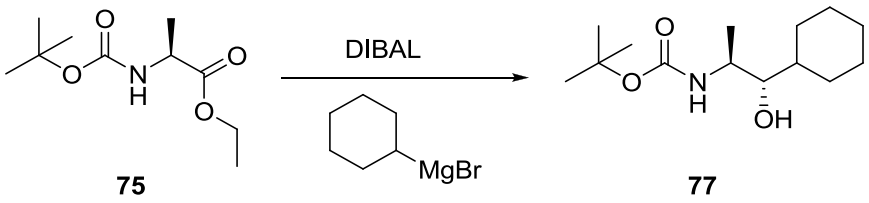
The starting material ethyl (2S)-2-[(diphenylmethylene)amino]propanoate **49b** (1 g, 3.55 mmol, 1 eq.) was left to dry overnight in the drying pistol under reduced pressure (2 mbar). Anhydrous DCM (20 mL) was added to the dried starting material under an inert atmosphere and transferred to a dry three-necked flask by cannula. The solution was left to stir and cool to -78 °C. A solution of DIBAL (0.69 M,[32] 10.28 mL, 7.1 mmol, 2 eq.) was added slowly *via* syringe pump. The solution was left to stir for 3 hours at -78 °C then warmed to -20 °C and left to stir for one hour. The solution was brought down to -78 °C and a dry pressure-equalizing dropping funnel was added in order to add the freshly made cyclohexylmagnesium bromide (0.41 M,[34] 26 mL, 10.65 mmol, 3 eq.). Once the addition finished, the reaction was left to warm to room temperature for 20 hours. The solution was quenched slowly by drop-wise addition of a saturated aqueous solution of $NaHCO_3$ (20 mL) at 0 °C. The product was extracted with DCM (3 × 30 mL), the combined organic layers dried over Na_2SO_4, filtered and concentrated into a yellow oil. The resulting oil was purified by flash chromatography (15-50% ethyl acetate/85-50% hexane). After further purification (10% ethyl acetate/ 90% hexane), recovered only the over reduced product **80** 223 mg (26 %).

^{1}H NMR: (400 MHz in $CDCl_3$) **δ** 7.39-7.17 (m, 10H), 5.03 (s, 1H), 3.54 (dd, 1H, J_1=14.8 Hz, J_2=6.8 Hz), 3.26 (dd, 1H, J_1=7.2 Hz, J_2=6.8 Hz), 2.77 (m, 1H), 2.19 (s, 1H), 1.06 (d, 3H, *J*=6.4 Hz)

^{13}C NMR: (100 MHz in $CDCl_3$) **δ** 141.90 (quaternary C), 140.70 (quaternary C), 128.6 (2C), 127.4 (2C), 126.3, 70.8, 63.3, 59.1, 19.0

HRMS M+H= 242.1540 calculated for $C_{16}H_{20}NO$ M+H=242.1539

Preparation of *tert*-butyl (1*S*,2*S*)-2-cyclohexyl-2-hydroxy-1-methylethylcarbamate 77:



75 **77**

Scheme 36: Synthesis of 77.

The starting material ethyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]propanoate **75** (1 g, 4.6 mmol, 1 eq.) was left to dry overnight in the drying pistol under reduced pressure (2 mbar). Anhydrous DCM (20 ml) was added to the dry starting material **75** under an inert atmosphere and transferred to the dry three-necked reaction flask by cannula. The reaction was left to stir and cool to -78 °C. A solution of DIBAL (0.66 M,[32] 13.9 mL, 9.2 mmol, 2 eq.) was added slowly *via* syringe pump. The solution was left to stir for 3 hours at -78 °C then warmed to -20 °C and left to stir for one hour. The solution was brought down to -78 °C and a dry pressure-equalizing dropping funnel was added in order to add the freshly made clyclohexylmagnesium bromide (0.41 M,[34] 33.7 mL, 13.8 mmol, 3 eq.). Once the addition completed, the reaction was left to warm to room temperature for 20 hours. The solution was quenched slowly by drop-wise addition of a saturated aqueous solution of $NaHCO_3$ (20 mL) at 0 °C. The product was extracted with DCM (3 × 30 mL), the combined organic layers dried over Na_2SO_4, filtered and concentrated which afforded a yellow oil. The resulting oil was purified by flash chromatography

(15-50% ethyl acetate/85-50% hexane). A mixture of diastereoisomers was obtained (400 mg, 33% yield) 3:1 in favour of the desired diastereoisomer. Further purification by chromatography was undertaken (10% ethyl acetate/90% hexane) which gave an oil of a single diastereoisomer **77** (80 mg, 6% yield) and also recovered a mixture of diastereoisomers (250 mg, 21% yield) 3:1 ratio in favour of the desired diastereoisomer.

^{1}H NMR: (single diastereoisomer, 400 MHz in $CDCl_3$ at 323K) **δ** 4.60 (br, 1H), 3.80 (m, 1H), 3.10 (br, 1H), 1.40 (s, 9H), 1.86 (m, 1H), 1.77 (m, 3H), 1.66 (m, 1H), 1.50 (m, 1H), 1.40 (m, 1H), 1.22 (m, 2H), 1.15 (d, 3H, *J*=5.6 Hz), 1.05 (m, 2H)

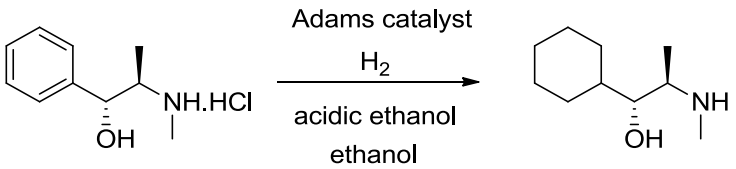
^{13}C NMR: (100 MHz in $CDCl_3$) **δ** 154.90 (C=O), 79.10, 77.90, 47.00, 40.00, 29.00, 27.80 (3 C), 25.90 (2 C), 25.7, 12.70

IR spectroscopy (Liq. cm^{-1}): 3438 (br, OH), 2925, 2852, 1693 (C=O), 1505, 1449

HRMS: M+H= 258.2061 calculated for $C_{14}H_{28}NO_3$ M+H=258.2064

$[\alpha]_D$= -7.6 (c=1, $CHCl_3$)

Preparation of (1*R*,2*R*)-1-cyclohexyl-2-(methylamino)-1-propanol 86:



85 **86**

Scheme 38: Synthesis of 86.

In a one necked flask, (1*R*,2*R*)-pseudoephedrine hydrochloride **85** (1.54 g, 7.626 mmol) was added as well as ethanol (10 mL). HCl saturated ethanol (0.1 mL) was then added to the solution and Adams catalyst (0.15 g, 0.661 mmol, 0.1 eq.). The reaction was hydrogenated (V_{H_2}= 0.54 L) overnight. The solution was filtered over celite under nitrogen and making sure that the catalyst does not become dry. The

filtrate was concentrated and then treated with a 1 M solution of aqueous $NaHCO_3$ until the aqueous layer was at pH=11. This aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give a white solid. The solid was then recrystallized in cold hexane, which gave white crystals of **86** (0.9 g, 71%).

^{1}H NMR: (400 MHz in $CDCl_3$) **δ** 2.98 (dd, 1H, *J*= 8, 2.4 Hz), 2.51 (m, 1H), 2.44 (s, 3H), 1.79 (m, 2H), 1.65 (m, 3H), 1.40 (m, 3H), 1.21 (m, 4H), 1.06 (d, 3H, *J*=6.4 Hz)

^{13}C NMR: (100 MHz in $CDCl_3$) **δ** 78.10, 56.00, 39.10, 32.80, 30.30, 26.20, 26.00, 25.80, 25.00, 15.20

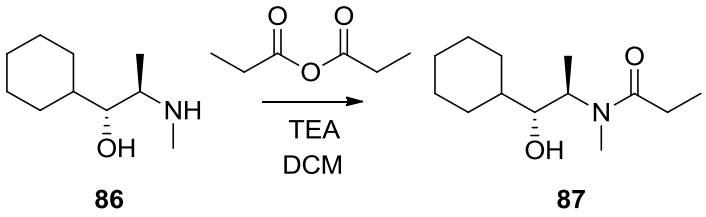
IR spectroscopy (KBr, cm^{-1}): 3310 (s, NH), 3163 (br, OH), 2976-2852 (alkyl),

HRMS: M+H= 172.1696 calculated for $C_{10}H_{22}NO$ M+H=172.1696

Elemental Analysis: $C_{10}H_{21}NO$ expected (%): C 70.1, H 12.4, N 8.2; found (%): C 69.8, H 12.1, N, 8.0

$[\alpha]_D$= -15.5 (c=1, $CHCl_3$). In the literature[43] the $[\alpha]_D$ of **86** is given as a salt in water **$[\alpha]_D$**= -9.05 (10% of the hydrochloride salt of **86** in water).[43] Unfortunately the analysis was not possible under these conditions as the apparatus gave a low energy.

Preparation of *N*-[(1*R*,2*R*)-2-cyclohexyl-2-hydroxy-1-methylethyl]-*N*-methylpropanamide 87:



86 **87**

Scheme 39: Synthesis of 87.

The (1*R*,2*R*)-1-cyclohexyl-2-(methylamino)-1-propanol **86** was dried overnight in a drying pistol under reduced pressure (2 mbar). Triethylamine was previously distilled as well as propionic anhydride. Anhydrous DCM was added to the dry amine **86** (0.106 g, 0.642 mmol, 1 eq.) and transferred *via* cannula to a dry three-necked reaction flask. Triethylamine (0.11 mL, 0.77 mmol, 1.2 eq.) was added to the solution followed by the addition of freshly distilled propionic anhydride (0.09 mL, 0.706 mmol, 1.1 eq.). The solution was left to stir under an inert atmosphere for 2 hours at room temperature. The reaction was quenched by addition of water (4 L. The organic layer was treated with a solution of aqueous $NaHCO_3$ (0.5 M, 2 × 3 mL) and an aqueous hydrochloric acid solution (1 N, 2 × 2 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated which gave **87** as a colourless oil. The crude material was purified by flash chromatography (50% ethyl acetate/50% hexane), which gave a colourless oil **84** (69 mg, 47%).

^{1}H NMR: (3:1 rotamer mixture, asterisk denotes minor rotamer, 400 MHz in $CDCl_3$) **δ** 4.50 (br, 1H), 3.90 (qd, 1H, *J*= 8.6, 6.8 Hz)*, 3.40 (br d, 1H, *J*= 8 Hz)*, 3.27 (br qd, 1H), 2.90 (s, 3H), 2.80 (s, 3H)*, 2.46 (m, 2H)*, 2.37 (q, 1H, *J*= 7.4 Hz), 2.36 (q, 1H, *J*= 7.4 Hz), 1.80 (br s, 4H), 1.67 (br s, 4H), 1.56 (br s, 2H), 1.45 (br s, 1H), 1.27 (br s, 11H)*, 1.17 (t, *J*= 3, 7.4 Hz), 1.16 (d, 3H, *J*= 6.9 Hz) minor rotamer of the two last methyls underneath the major one.

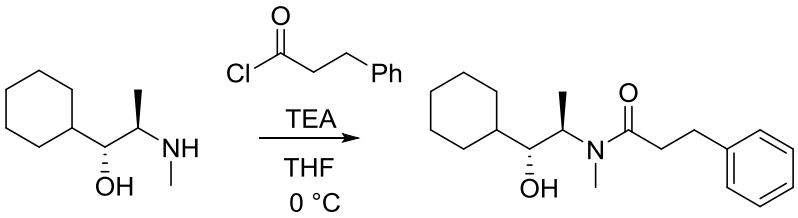
^{13}C NMR: (100 MHz in $CDCl_3$) **δ** 175.80 (C=O), 77.50, 54.30, 40.50, 31.10, 30.50, 27.50, 26.50, 26.60, 26.40, 26.10, 14.50, 9.20

IR spectroscopy (NaCl, cm^{-1}): 3411 (br, OH), 2927, 2852, 1625 (C=O), 1449

HRMS: M+H= 228.1958 calculated for $C_{13}H_{26}NO_2$= 228.1958

$[\alpha]_D$= 31 (c=1, $CHCl_3$)

Preparation of *N*-[(1*R*,2*R*)-2-cyclohexyl-2hydroxy-1-methylethyl]-*N*-methyl-3-phenylpropanamide 88:



86 **88**

Scheme 40: Synthesis of 88.

The (1*R*,2*R*)-1-cyclohexyl-2-(methylamino)-1-propanol **86** was dried overnight in a drying pistol under reduced pressure (2 mbar). Anhydrous DCM (2 ml) was added to the dry amine **86** (0.094 g, 0.569 mmol, 1 eq.) and transferred by cannula to a dry 3 necked reaction flask. Triethylamine (0.1 mL, 0.74 mmol, 1.3 eq.) was then added to the solution. The reaction was left to stir at 0 °C whereupon fresh hydrocinnamoyl chloride (0.097 mL, 0.654 mmol, 1.15 eq.) was added drop-wise. The solution was left to stir under inert atmosphere for 2 hours at 0 °C. The excess acid chloride was quenched with water (4 mL). The organic layer was extracted with ethyl acetate (3 × 5 mL) and washed with brine (2 × 5 mL). The combined organic layer were dried over Na_2SO_4, filtered and concentrated to give a colourless oil. The crude material was purified by flash chromatography (50% ethyl acetate/50% hexane) which gave a colourless oil **88** (69 mg, 17%).

^{1}H NMR: (3:1 rotamer mixture, asterisk denotes minor rotamer, 400 MHz in $CDCl_3$) **δ** 7.33-7.20 (m, 10H, mix of rotamers), 4.52 (br s, 1H)*, 3.89 (qd, 1H, *J*= 8.6, 7.0 Hz)*, 3.40 (br d, 1H, *J*= 8.8 Hz)*, 3.27 (br s, 1H), 2.99 (t, 2H, *J*= 7.6 Hz) other rotamer just underneath, 2.88 (s, 3H), 2.83 (s, 3H)*, 2.66 (t, 2H, *J*= 7.6 Hz)*, 2.65 (t, 2H, *J*= 7.6 Hz), 1.80 (br s, 4H), 1.67 (br s, 2H), 1.55 (br s, 5H), 1.25 (br s, 11H)*, 1.15 (d, 3H, *J*= 6.8Hz), 1.07 (d, 3H, *J*= 6.8 Hz)*

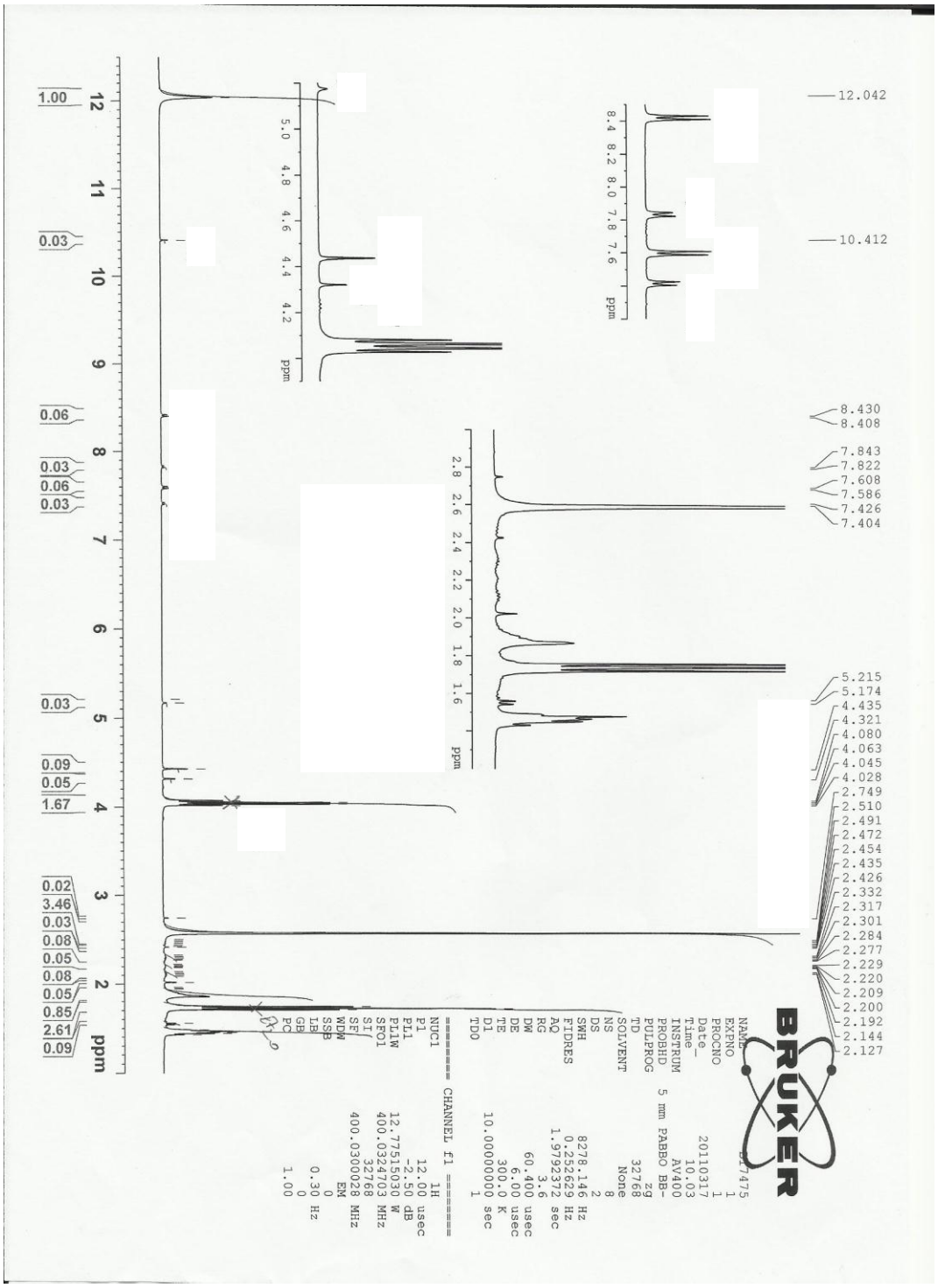
^{13}C NMR (100 MHz in $CDCl_3$) **δ** 175.80 (C=O), 140.80 (quaternary C), 127.99 (2 C), 127.90 (2 C), 125.60, 86.42, 76.90, 39.90, 35.60, 34.90, 31.10, 30.70, 30.20, 26.00, 25.90, 25.60, 14.00

IR spectroscopy (NaCl, cm^{-1}): 3413 (br, OH), 2926, 2852, 1624 (C=O), 1451, 699

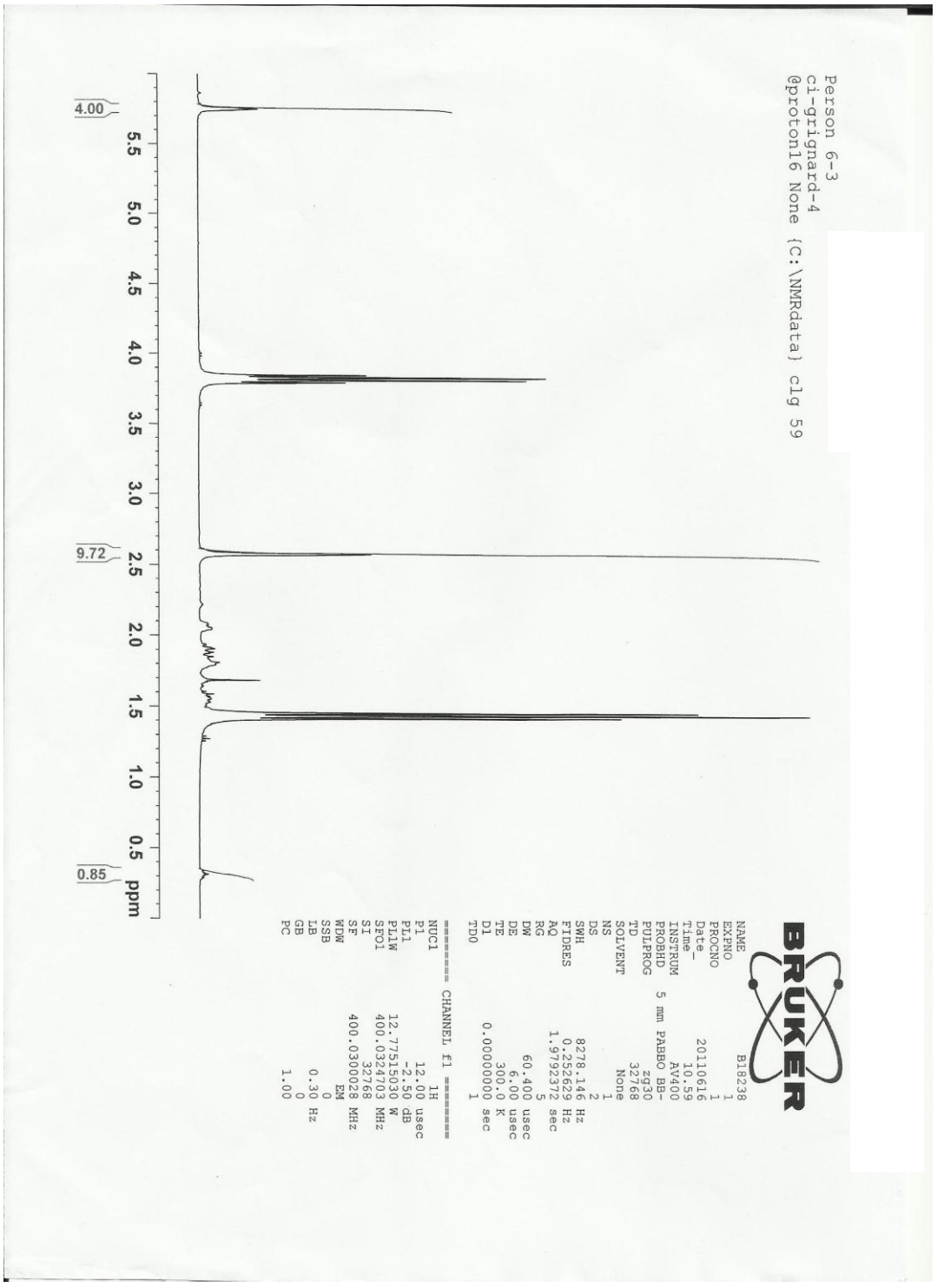
HRMS: M+H= 304.2270 calculated for $C_{19}H_{30}NO_2$= 304.2271

$[\alpha]_D$= 23.8 (c=1, $CHCl_3$)

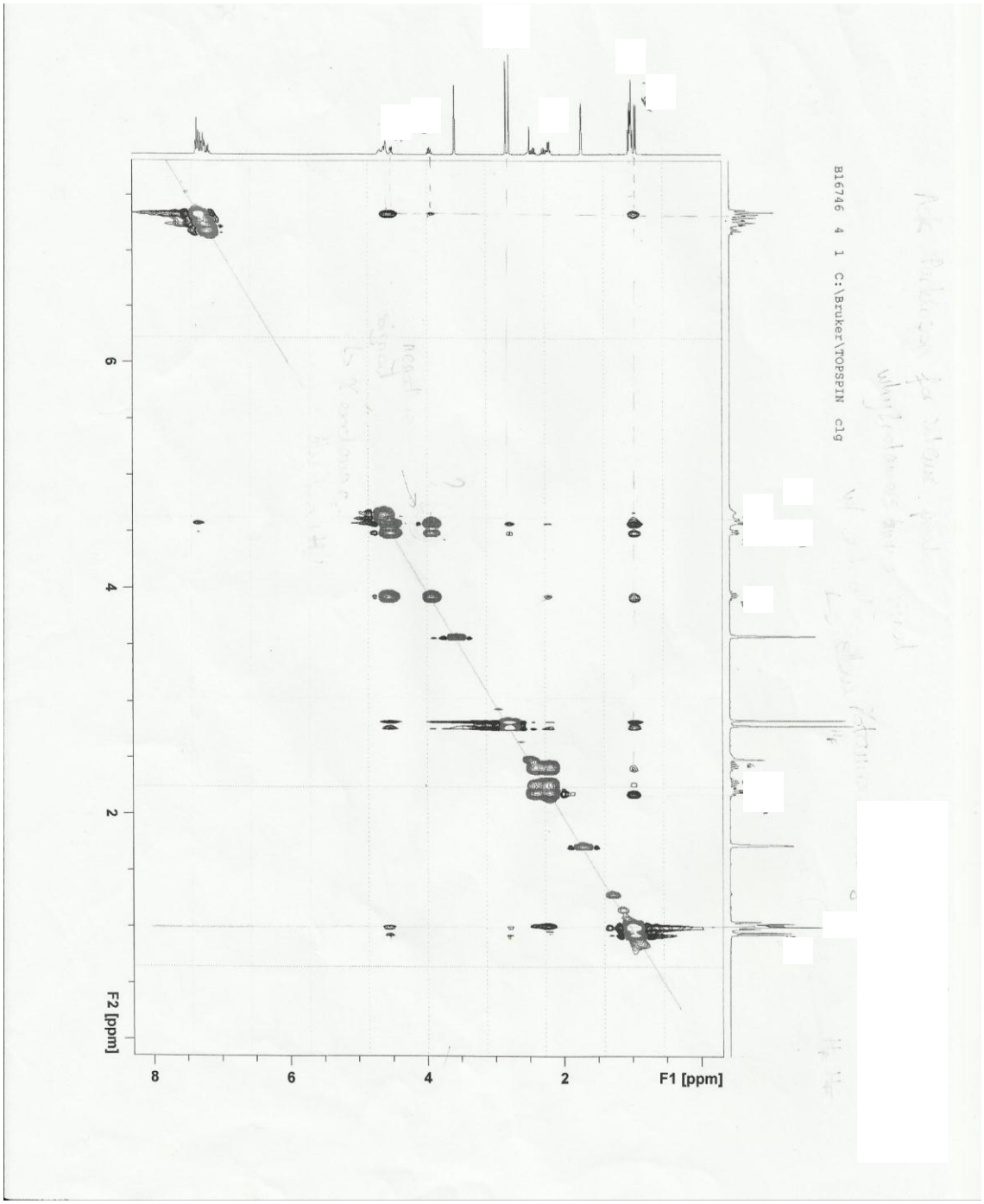
Appendix 1: NMR for titration of DIBAL



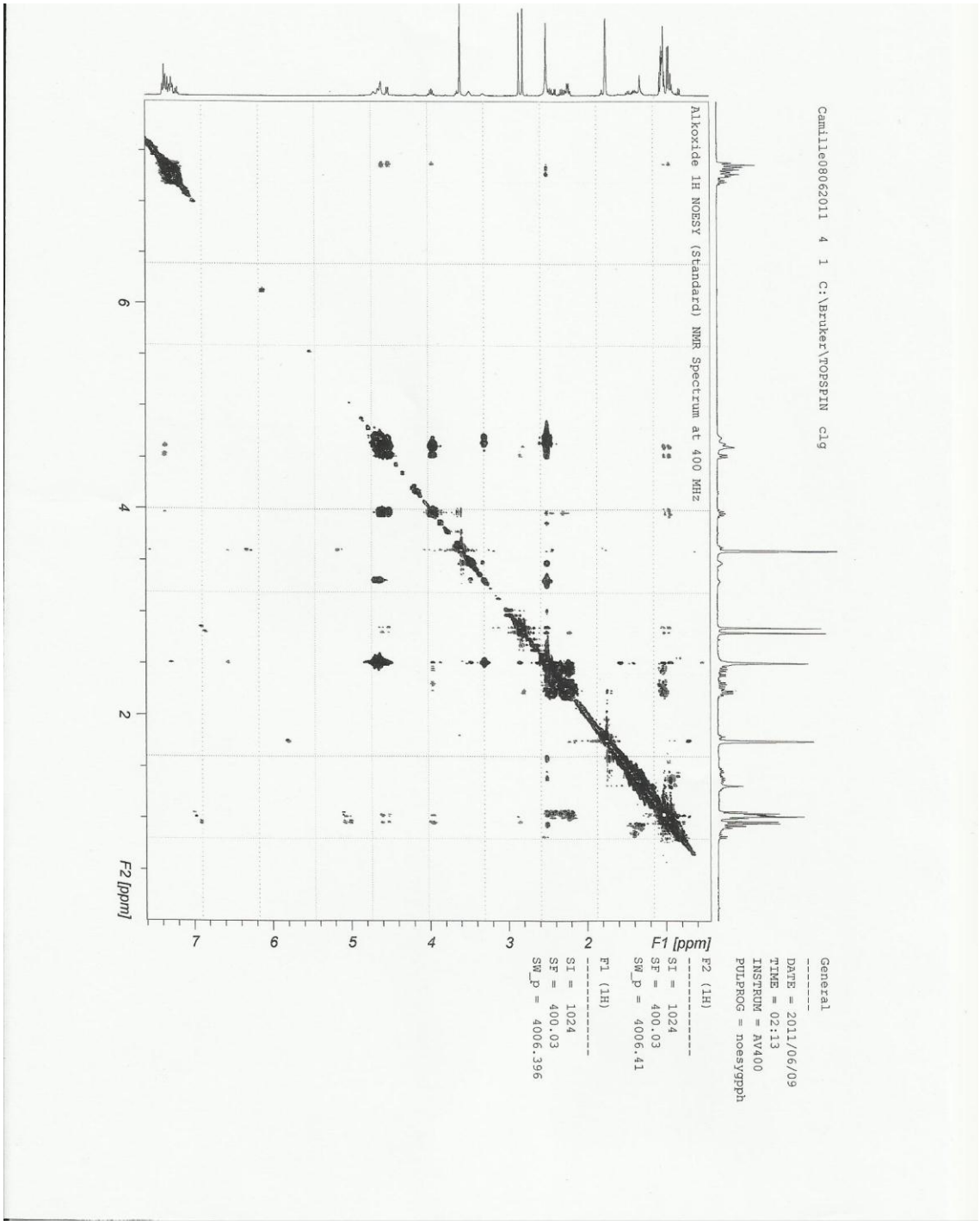
Appendix 2: NMR titration Grignard 82



Appendix 3: NOESY of amide 28



Appendix 4: NOESY of alkoxide 28a



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